CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 1 *number* 4 **July-August 1960**

Editorial

Therapeutics

The science of therapeutics has the deepest roots in medical antiquity. Despite its tradition, however, therapeutics has not achieved a growth comparable to that of pathology, physiology, or even diagnosis in medicine. Despite the highly efficacious therapeutic agents and maneuvers that have been discovered over the years, progress has been faltering and, until recently, not very solidly based on the scientific method. Indeed, changes in therapy have evolved as often from fashion as from evidence and sometimes the treatment of choice of today is the malpractice of tomorrow. Thus, in different eras venesection and transfusion have been practiced for the same condition and with the same ends in mind. Eugene DuBois took cognizance of the slow pace of therapeutic research in his presidential address to the Association of American Physicians in 1938. According to DuBois,[3] ". . . any young neophyte can introduce a new drug. It requires a man of large experience and considerable reputation to destroy an old one." Barr,[1] in an essay entitled "The Price We Pay," calls attention to the tragically harmful effects of many hastily evaluated but assiduously applied therapies.

The secret of potential progress and ultimate strength in the science of therapeutics lies in the controlled therapeutic trial, recently hailed by Pickering[5] as the most significant development in medicine during the past decade. Actually, the practice of the controlled therapeutic trial goes back at least to 1863 when Béclard[2] put to the test the practice of blood letting for pneumonia. From his careful experiment he concluded that blood letting was of no value to the patient. Little attention was paid either to his scientific contribution of proposing the controlled therapeutic trial or to the specific findings of his study. The practice of blood letting was continued, and in 1909 William Osler,[4] widely known as a therapeutic nihilist, recommended venesection for the treatment of pneumonia. Even after the conclusion of World War I, the leading clinicians of the United States were still convinced of its value. Thus is provided an impressive example of the truth of DuBois' remark about destroying an old therapy.

Experimental medicine has made impressive gains since the days of Béclard but in therapeutics too often post hoc reasoning has led to false inferences. Investigators

have been deluded by the seeming simplicity of the therapeutic situation with its "before," "during," and "after." There has been a failure to recognize the elements of proper design, the meaning of controls, and what constitutes adequate evidence of therapeutic efficacy. In contrast to those concerned with the health of humans, agriculturists have reaped rich rewards from the controlled experiment. They have recognized the importance of selecting normal populations, of randomizing, of limiting variables, and other statistical precautions. In medicine, on the other hand, inferences have been drawn by leading clinical investigators from inadequately designed therapeutic experiments. Thus aureomycin was thought to be effective in the treatment of atypical pneumonia on the basis of a comparison of one year's cases with previous experience with the disease. A control group for sympathectomy in the treatment of essential hypertension was made up from those who refused the operation, and a control group for the anticoagulant treatment of myocardial infarction was given no pills and was subjected to no frequent repeated venepunctures.

A major reason for the invalidation of much published data in therapeutic research has been failure to take into account the placebo effect. Nevertheless, neither placebos, important as they are, nor careful statistical analysis of data can correct errors in selection of patients or errors in experimental design. The time has come for the editors of our journals to apply the necessary criteria. Perhaps this journal will contribute richly toward the understanding of proper design and control in therapeutic research. By demanding high standards it may encourage workers to clearer thinking and through emphasis on excellence actually recruit new and critical investigators into the field.

References

1. Barr, D. P.: Hazards of Modern Diagnosis and Therapy—the Price We Pay, J.A.M.A. **159**:1452-1456, 1955.
2. Béclard, M. J.: Rapport général sur les prix décernés en 1862, Mém. Acad. méd. Paris **26**: xxxii-xlviii, 1863.
3. DuBois, E. F.: Elimination of Worthless Drugs, Trans. A. Am. Physicians **54**:1-5, 1939.
4. Osler, W.: The Principles and Practice of Medicine, ed. 5, New York, 1903, D. Appleton & Company.
5. Pickering, G. W.: Concepts of Medical Education Abroad as They Relate to Cardiovascular Teaching—and—Modern Concepts in the Teaching of Cardiopulmonary Function and Disease, Rep. Fifth Conf. Cardiovascular Training Grant Program Directors, Williamsburg, Virginia, 1958, p. 11.

Stewart Wolf, M.D.

Commentary

The use and misuse of statistics in medical publications

Research workers' widespread lack of understanding of the rationale of statistical techniques, and the frequent use of statistical tests as a substitute for thoughtful investigational design, meticulous work, and repetition of experiments, justify the antagonism to statistics exhibited by some experimenters. To one who has had personal experience of the way in which statistical thinking, as distinct from statistical arithmetic, can promote good investigation, this perversion of statistics is lamentable. It appears to be due, not so much to investigators themselves, but to the order in which experimenters' statistics was developed by the pioneers and presented to research workers, because Fisher's "Statistical Methods" (1925), which discussed chiefly significance tests, preceded by ten years his "Design of Experiments," which showed how to plan experiments in order to obtain unambiguous inferences from the tests.

Other causes of misunderstanding are discussed, and, in an effort to promote a more rational attitude to statistics, nine suggestions are presented.

Donald Mainland, M.B., D.Sc.* *New York, N. Y.*
Department of Medical Statistics, New York University School of Medicine

"Medical papers now frequently contain statistical analyses, and sometimes these analyses are correct, but the writers violate quite as often as before, the fundamental principles of statistical or of general logical reasoning." This was written by Major Greenwood,[5] the English medical statistician, in 1932, in the interval between the appearance of the two books by R. A. Fisher (now Sir Ronald Fisher) that have been chiefly responsible, directly or indirectly, for the spread of statistical techniques among experimenters—*Statistical Methods for Research Workers* (1925)[3] and *The Design of Experiments* (1935).[4] The techniques have entered every field of pure and applied science; and yet in 1950 Lancelot Hogben,[7] the experimental biologist who has become a medical statistician, could assert, without fear of serious contradiction, that "less than 1 per cent of re-

This paper was written as part of a project entitled "Promotion of Biometrical Methods in Medical Research," supported by a grant, RG-6100, from the National Institutes of Health, U.S. Public Health Service.

*Address, 550 First Avenue, New York 16, N.Y.

search workers clearly apprehend the rationale of statistical techniques they commonly invoke."

The spread of statistics

During the decade since Hogben wrote, statistical techniques have continued to spread. In medicine two prominent examples are controlled clinical trials, and the search for causal factors in chronic diseases by a method which is called "epidemiologic," but is that of sample-survey statistics.

The spread of statistics is, however, something more than the increased use of experiment designs and arithmetic tests. A book entitled *An Introduction to Scientific Research,* published in 1952 by E. Bright Wilson,[13] a professor of chemistry, is essentially an application of statistical thinking to the performance of laboratory experiments. In *The Common Sense of Science,* Bronowski,[1] an applied mathematician, writes: "This [statistics] is the method to which modern science is moving. . . . This is the revolutionary thought in modern science. It replaces the concept of *inevitable effect* by that of the *probable trend.*"

Perversion of statistics

To a medical research worker who, soon after the first appearance of Fisher's *Statistical Methods,* started using the new ideas and techniques in his own work, saw their relevance to all medical research, and gradually obtained the label "statistician," the triumph of statistics in the past thirty years might be expected to bring unalloyed pleasure. It does not. His impression, from reading medical literature and acting as consultant or collaborator in research, is that, although statistical thinking has spread, the misuse of statistical arithmetic has spread faster. It sometimes occurs to him that he might increase his income considerably by a standing bet with all contributors to certain prominent medical journals that their statistical tests were either unnecessary, misapplied, or misinterpreted; and there would be little additional risk in keeping the bet open for articles in which a statistician's name appeared in the acknowledgments or even among the coauthors. Unfortunately, the evidence on which the bets could be decided would often be missing. Procedures, circumstances, and events in an investigation may seem so unimportant to the investigator that he may not even remember them, and yet, if known, they might render the statistical analysis ridiculous.

The foregoing paragraph sounds like the usual statistician's criticism of investigators. On the contrary, it expresses a lament that a method of thinking, planning, and action which could lead to a better investigation is often perverted, so that it becomes a set of gadgets that do more harm than good. This was doubtless what impelled a biochemist to declare recently that one cannot be a biostatistician and a good biochemist, for he had observed a phenomenon that has become common in laboratory publications. The verdict of a small-sample significance test, whether it is "significant" or "not significant," appears very convincing to those investigators, editors, and manuscript reviewers who do not know how little it really tells them. Therefore, a significance-test devotee can achieve a much higher manuscript acceptance rate per unit of time than one who tests his first results by abundant repetition of his experiments. Significance testing thus becomes a substitute for thought, clean experimentation, and perseverance. Worse still, I have seen careful and critical experimenters, long resistant to statistical tests, become converted, and then draw from their tested data inferences which, in the days before their conversion, they would rightly have greeted with derision.

A cause of perversion. A clue to one cause of the perversion of statistics can, I believe, be found in the order of publication of Fisher's two principal books on the subject. *Statistical Methods* was concerned very largely with the presentation of significance tests—devices whereby an investi-

gator could discover how often random (pure chance) variation, as in card shuffling or in taking of samples from a box containing thoroughly mixed uniform disks, would produce differences of the magnitude that he met in his investigations. *The Design of Experiments* ten years later showed how to set up experiments in order to utilize this knowledge of the results of chance—how to make chance work for us, e.g., by card shuffling or the use of random numbers in assigning treatments to subjects, so that at the end of an experiment we could say: "The cause of the observed difference in outcome was either the randomization or the factors [fertilizers, drugs, or the like] that we introduced. The randomization has taken care of the effects of the innumerable, often hidden, factors that we did not eliminate (or balance in some systematic fashion) at the outset."

The order of appearance of Fisher's two books represented the development of knowledge and methodology by pioneers; but it gave statistical arithmetic a ten years' lead on statistical design, and even after *The Design* appeared, this lead was maintained or increased. Although *The Design* presented fundamental principles, applicable to a wide variety of experiments, its chief flavor was agricultural, because that was the area where the theory and methods had been worked out. To many medical laboratory workers whose predecessors had for generations been designing experiments which had led medicine from empiricism into science, there seemed little need for trying to apply to their work the principles enunciated by an agricultural statistician whose lines of thought and style of presentation made comprehension difficult even for statisticians.

Moreover, scientific methodology in the abstract is not interesting to many people, whereas techniques, which seem to have an immediate practical application, gain readier attention. Laboratory workers and clinical scientists came increasingly in contact, through statistical "cookbooks," with such techniques—statistical test recipes, both those that Fisher had invented and earlier recipes, which had originated with statisticians such as Karl Pearson. Thus there started the epidemic of statistical arithmetic. At first sight, investigators might appear to blame; but were they?

Assumption of random variation

In trying to answer that question it is interesting to look at the earliest and most familiar of the "small-sample" techniques, the *t* test, demonstrated by "Student" (the brewery chemist, W. S. Gosset) in 1908.[12] As an example of the application of the *t* test, "Student" used data of Cushny and Peebles[2] from research on the sleep-inducing properties of hyoscyamine and hyoscine; and Fisher used the same data as his principal example of the *t* test in *Statistical Methods*. Because "Student" apparently miscopied the names of the drugs in his paper we shall label the compounds "A" and "B," as did Fisher after the first few editions of his textbook. Each of 10 patients received drugs A and B on different occasions, and the numbers of hours of sleep after administration of each drug were recorded. The data to be tested, therefore, comprised ten B — A differences in hours of sleep, and "Student's" conclusion from the *t* test was that the odds were about 666 to 1 that B was a better soporific than A.

One of the assumptions underlying this conclusion, although not explicity stated, was that the experiment had been so conducted as to control, as if by card shuffling or disk sampling, the effects of all the factors, except the drug difference, that could cause a B — A difference—in other words, that the intersubject variation in the B — A differences was strictly random variation. In Fisher's presentation the difference was described as "clearly significant" since the *t* value obtained from the sample was 4.06 and [illegible] degrees of freedom "only one value [illegible] hundred will exceed 3.250 by chance." This statement does not, in so many words, attribute the difference in outcome to the difference in drugs, but the

inference is implied, and it becomes even more evident in Fisher's discussion of the signs of the ten B — A differences, of which 9 were positive, one difference being zero. He wrote: ". . . if the two drugs had been equally effective, positive and negative signs would occur with equal frequency." Here was the same implicit assumption that "Student" had made—that the experiment had been so conducted that nothing could have caused the B — A differences except chance and the drug difference. The nature of this assumption, and how to make it more than an assumption by randomization, became clear in *The Design of Experiments,* but the same wording of the statement about positive and negative signs in Cushny and Peebles' data has continued into the latest (1954) edition of *Statistical Methods.*

This comment is not hair-splitting semantics; nor is the example unique. The "prime object" of *Statistical Methods* was "to put into the hands of research workers, and especially biologists, the means of applying statistical tests accurately to numerical data accumulated in their own laboratories or available in the literature." The reader who used the book for laboratory reference was cautioned to "work through, in all numerical detail, one or more of the appropriate examples, so as to assure himself, not only that his data are appropriate for a parallel treatment, but that he has obtained some critical grasp of the meaning to be attached to the processes and results." This sounds like an excellent safeguard; but, in fact, this thorough study of the examples leads the investigator no nearer to the "meaning to be attached to the results" than did "Student's" or Fisher's treatment of Cushny and Peebles' data. It leaves to the opinion (or faith or desire) of the investigator the decision that effects found in his data are due only to the factors he is testing plus chance (strictly random error). For my part, I would be much more ready to accept, without any test at all, an experimenter's opinion that an observed difference between two sets of measurements would rarely (or commonly) occur if he wrote the measurements on cards and shuffled them a thousand times, than I would be to accept his opinion that his method of assigning treatments had been "equivalent to" randomization.

"Random variation" seems to be often considered synonymous with "whatever variation the research worker has not taken care of by a systematic investigational scheme such as stratification, or by subsequent arithmetic, such as covariance adjustment." Such ideas have probably arisen from our rather loose concepts of "chance" as comprising a multitude of causal factors that we cannot, or do not, identify. The same line of thinking probably accounts for the impression which some investigators still retain, that a significance test is a magic device for determining whether there was, or was not, some hidden bias in their investigation—as if a small value of P means a small probability of bias. This perhaps explains the description of the function of a statistician that a research worker suggested recently, as follows: "Most of us are not Claude Bernards; therefore we need a statistician to tell us whether our conclusions are probably right or probably wrong."

The *Statistical Methods* pattern of presenting techniques has been imitated by most of its simplified successors, and it is still often imitated by statistical writers in medical journals who present recently developed techniques. Therefore, the laboratory workers who in 1960 affirm that all they require from a medical statistician are mathematical formulas and computing services can point for their defense to a tradition sanctioned by the founders of experimental statistics and confirmed by their followers.

Sometimes I wonder whether the spread of perverted statistics would have been arrested if in 1935 *Statistical Methods* had been rewritten, with the fundamental ideas from *The Design of Experiments* attached to every numerical example, or if a fraction of the time spent by medical investigators and their helpers during the past

quarter of a century on statistical arithmetic had been devoted, instead, to the study and application of the main ideas contained in the first half-dozen chapters of *The Design of Experiments.*

Experimental proof and significance testing

Some of us who have been acquainted with *The Design* throughout its career dip into its first few chapters again from time to time and discover statements that have more meaning for us now than they had on the first (or sometimes the tenth) reading. In sect. 7, for example, is the following passage: "In order to assert that a natural phenomenon is experimentally demonstrable we need, not an isolated record, but a reliable method of procedure . . . we may say that a phenomenon is experimentally demonstrable when we know how to conduct an experiment which will rarely fail to give us a statistically significant result." If instead of "a statistically significant result" we used a phrase such as "a result in the same direction and of similar magnitude," Fisher's statement would express a fundamental part of the philosophy of experimentation, and would be remarkably like one of the strongest criticisms that experimenters aim at statistics.

The quotation must seem rather strange to those who think of Fisher as the creator and deifier of significance tests; but it acually reveals rather well the attitude that he has displayed in personal communications and in various written statements. Those workers for whom $P = 0.05$ has become a rigid stop-and-go sign might profitably reread his remarks on first presenting his table of P values for chi square (*Statistical Methods,* sect. 20): "In preparing this table, we have borne in mind that in practice we do not want to know the exact value of P for any observed χ^2, but, in the first place, whether or not the observed value is open to suspicion. If P is between .1 and .9 there is certainly no reason to suspect the hypothesis tested. If it is below .02 it is strongly indicated that the hypothesis fails to account for the whole of the facts. We shall not often be astray if we draw a conventional line at .05, and consider that higher values of χ^2 indicate a real discrepancy."

Fisher's view could, I think, be fairly expressed as follows: Significance tests are useful tools to *help* an investigator to decide what to do next—not to *tell* him what to do. His data may show "no reason to suspect the hypothesis tested," but "the null [no-difference] hypothesis is never proved or established, but is possibly disproved, in the course of experimentation" (*Design of Experiments,* sect. 8); and the investigator may have good reasons for not dropping the search. He can then increase the sensitiveness of his experiment quantitatively by taking a larger sample (*Design,* sect. 11) or qualitatively by reorganizing the structure of his experiment or by refining its technique (*Design,* sect. 12), or, of course, by all three methods.

Confidence limits

Even more useful than a significance test as a help for the investigator in deciding what to do next, and in revealing to him how little his data tell him, is an answer to the question: If, despite there being no proof of a difference (e.g., between the effects of two drugs) a real difference exists, how large or how small may it be? Although not expressed so simply, this was the kind of question that was answered in Fisher's discussion of the probable limits of a mean difference (*Design,* sect. 62), and it is unfortunate that this matter, so important to research workers, became obscured by arguments among statisticians regarding differences in the reasoning processes underlying "fiducial" limits and "confidence" limits.

Nine suggestions for developing a more rational attitude to statistics

As time goes on, more investigators will learn to distinguish the counterfeit, useless, or dangerous from the genuinely scientific

and useful elements in statistical procedures; but gadgets and bad habits spread more easily than does critical thinking, and unless we make positive efforts improvement will be slow. As an attempted contribution to such efforts, nine suggestions have been prepared.

Some statisticians may dislike the criticism implied in some of the remarks, but I believe that many of them will agree that it is better to encourage, and try to answer, penetrating questions, than to wait until investigators discover for themselves the spurious elements in statistical practice and by their criticism cast suspicion on all statistics. Hogben's[8] recent attack on Fisherian and other statistics is so wholesale and so difficult for many research workers to follow, that statisticans probably need have little fear of its consequences. But I doubt whether the same equanimity could be maintained if some research workers, well acquainted with the real meaning of statistical tests, estimates, assumptions, and predictions, were to go in detail through a number of investigations in which statistical help had been obtained, and were then to describe, in terms that other research workers could understand, the details of the investigations, the statistical analyses, and the conclusions that had been drawn.

The nine suggestions that may help us to develop a more rational attitude to statistics are as follows:

I. Avoidance of preconceptions and prejudice. To obtain a fresh look at statistics, we should try first to get rid of our preconceived ideas about it and our prejudices either against it or in its favor.

II. Knowing what we are doing. If we are going to use statistical ideas and the resulting techniques in the design, conduct, and analysis of our investigations, and yet retain the title "investigator," it seems essential that we know what we are doing, and why we are doing it. Statistical thinking is, essentially, thinking about variation (i.e., differences between things, events, or phenomena that bear the same label) and about the methods of dealing with variation; and if we are content to let someone else do this thinking and tell us what to do, we are, it seems to me, accepting the role of technician.

III. Experiments and surveys. A useful way of starting to clarify our thoughts about analysis and inference is to distinguish between an experiment, in the strict sense, and a survey. In an experiment, in the strict sense, we assign the factors under test *at will* to the individuals that comprise our experimental material (patients, animals, or bacterial culture tubes); therefore, we can assign by a method (randomization) which leads to the "either chance or the factors under test" type of inference.

Most clinical researches and many laboratory investigations are not experiments in the strict sense, because we do not (often cannot) assign the factors under test (e.g., diseases) at will. Such investigations are best called "surveys," however small the sample size and however complex the procedures to which we subject our material. We may speak, loosely, of "Nature's experiments" in the assigning of diseases or other features, and there is always some randomness (several factors acting independently of each other) in such phenomena; but Nature does not try to randomize, and we know, from card shuffling, disk sampling, and the like, what prolonged efforts are necessary to remove trends and clusters. Therefore, although we may, for practical purposes, choose to accept the results of a survey as a demonstration of a causal relationship, we should remember that a survey, or even a million surveys on the same topic, can demonstrate only an *association* between the factors under test and the phenomena they seem to cause.

IV. The basis of statistical arithmetic. Whenever we use statistical arithmetic we should insist on seeing as clearly as possible the reasoning and knowledge on which it is based. This does not mean trying to understand the mathematical proof of a formula, because mathematical proof is no proof that the formula is safe in the real world.

To illustrate, let us suppose that we have conducted a clinical trial, after randomization (e.g., by card shuffling) of drugs A and B to 20 patients each, and that we emerge with 16 "successes" in the A group and 10 in the B group. The question that we wish our significance test to answer is this: If we performed a large number of card shuffling trials, always with 40 cards, 26 marked "S" (success) and 14 marked "F" (failure), and in each trial dealt them into two piles, 20 A's and 20 B's, in what percentage of trials would we find as strong apparent evidence of an A-B difference as we did in our clinical trial, i.e., 16 (or more) S's in one pile and 10 (or fewer) in the other pile? We have, of course, already decided that if this percentage is less than 5 per cent (or less than 1 per cent or some other figure), we are going to accept it as evidence that the randomization in the clinical trial did not account sufficiently for the observed difference in outcome.

Testing fourfold frequency tables. There are four ways in which we could find the required percentage of random arrangements:

A. We could actually perform the card shuffling trials, say a thousand or more. This would be time consuming; but in more complex problems, where we have no mathematical short cuts, this Monte Carlo ("gambling") method is much used.

B. We could write out all the possible arrangements of 26 S's and 14 F's in two groups of 20, and find the percentage of these arrangements that met our requirements—16 or more S's in one group, 10 or fewer in the other group. At this point we should watch our reasoning. We would be implying that, if we performed card shuffling trials, each of the possible arrangements, which we had written out, would occur with equal frequency—more exactly that, as we continued the shuffling trials, we would find that the percentage frequencies of each of the possible arrangements would approach equality. The reason for this belief is based on some centuries of experience of games of chance.

C. The writing out of all possible arrangements is, of course, not practical, because their number, even with these small samples, would run into many millions; but fortunately we can obtain the information that we need by a mathematical method, which is based on the discovery, made about the end of the seventeenth century, that the binomial expansion represents what is found in certain kinds of games of chance.

In the fifth (1934) edition (sect. 21.02) of *Statistical Methods,* Fisher showed how to use the binomial expansion for problems like our two-sample success-failure data. His "exact test for 2×2 tables" enables us to find, not the millions of possible individual arrangements, which we do not need to know about, but the percentage frequencies of the various classes of these arrangements, such as 16 S's in one sample of 20 with 10 S's in the other sample, 17 and 9, 18 and 8, etc. The easiest way for an experimenter to obtain insight into the method is to take an imaginary group of, say, 8 subjects containing 5 S's and 3 F's, and write out all the possible ways (70) in which two samples of 4 subjects can be formed. It will be found that 14.286 per cent of these arrangements contain 4 S's in one sample and 1 S in the other, while 85.714 per cent contain 3 S's in one sample and 2 S's in the other—exactly the proportions found by applying the "exact" method, either from Fisher's description or from more detailed arithmetic instructions.*

D. The "exact" method is rather laborious, and therefore the chi-square test for 2×2 tables is commonly used instead. This was devised, before the "exact" test, for comparing two samples taken at random from the same "infinite" population; that is, the conditions are not quite the same as the random assignment of a specified number of S's and F's in two finite samples. Therefore, in order that we may trust the chi square test as a substitute for the exact test,

*For example, Mainland,[10] p. 274.

we require empirical evidence—numerous comparisons of the two tests. Such comparisons[9,10] have shown that chi square with "Yates' correction" is, with rare exceptions, a safe test for significance at the 5 per cent and 1 per cent levels if we demand a chi square value greater than 4 as an indication of P less than 0.05 and a value greater than 7 as an indication of P less than 0.01. The rare exceptions are easily detected by applying certain precautions.[10] Even the arithmetic of chi square, and the residual doubts regarding its safety, can be avoided for pairs of equal samples containing up to 500 individuals in each sample, and for unequal samples up to size 20, by merely taking our data to published tables.[11]

Testing measurement data. As we have seen, it is not very difficult to appreciate what is going on in a 2×2 table frequency comparison. In other statistical arithmetic, especially tests of, and estimations from, measurement data, we run into assumptions. Worse still, we often do not run into them; we are either not told about them, or we are told about them so cryptically that we do not appreciate their implications.

One of the assumptions made in many statistical tests and estimates is the Gaussian frequency-curve assumption; e.g., tables for use in the *t* and F tests are derived from mathematically exact Gaussian distributions.

An assumption that is often involved in the interpretation of tests is the "homogeneity" of variation within the different groups that are compared or combined—that is, the assumption that the intragroup variation does not differ from group to group more than in random samples from the same population.

In making estimates after regression analysis many investigators hardly seem to be aware that they are assuming a straight-line relationship—an assumption which, if they really thought about the phenomena under study, they might seriously question.

Strictly speaking, the assumptions are that our measurements do not depart from the prescribed conditions (the Gaussian curve, equality of variation, linearity of regression, and so on) enough to vitiate our tests and estimates. Therefore, it might be supposed that if we apply tests to our data (e.g., a test for skewness or for difference in intrasample variation) and obtain a nonsignificant result, the assumptions will be safe; but this is by no means true.

Although the Gaussian assumption is perhaps not as dangerous as others, at least when it is involved in the comparison of mean values, we can use it as an example, because its defenses are multiple.

THE GAUSSIAN ASSUMPTION. First, we may recall the remark that has been attributed, in various forms, to several different authors: "Everybody believes in the Gaussian law—the experimenters because they think it can be proved by mathematics, the mathematicians because they think it has been established by observation." We shall look at three defenses of the Gaussian assumption:

A. It has been shown that if the variation between measurements is caused by factors that are independent of each other, even if the factors are few in number (four or five), the frequency distribution resembles a Gaussian distribution.

B. It has been shown mathematically that, whatever the shape of the frequency distribution in the parent population of measurements, when random samples of the population are taken, the frequency distribution of the *means* of those samples becomes more and more nearly Gaussian in shape when the sample sizes are increased.

C. Textbooks and statisticians often assure us that explorations of data have shown that we shall "seldom be led astray" if, under certain (rather loosely defined) conditions we use tests or estimates derived from the Gaussian distribution.

These explorations sound analogous to the exploration that has given us confidence in the 2×2 chi square; but the situation is very different. In testing chi square, randomization trials or display of all possible arrangements was not necessary, because

Fisher's "exact" test gave the required information; but when we have a set of measurements and wish to make all possible arrangements of them in two or more samples of a specified size, there is no mathematical short cut to the exact results. Except with extremely small samples, this permutation labor is too heavy; therefore randomization is employed instead. By the use of random numbers the cards bearing the measurements are arranged in two samples (or in more than two samples when the F test is being studied), and the t (or F) test is applied. This is repeated, say 1,000 times, to find whether the various t (or F) values occur approximately with the frequencies required by the Gaussian distribution theory.

The other great advantage in the validation of chi square is the simplicity of the data. We are concerned simply with the numbers of X's and not-X's, whatever X may stand for; and a pattern of agreement between chi square and the "exact" test quickly emerges—for example, the agreement improves as the X's and not-X's become more nearly equal in number. By contrast, possible varieties of samples of measurements are innumerable. Therefore, we may laboriously validate t or F for one set of measurements but feel no safety in applying the results to a set of measurements of a different kind, even if sample sizes are the same as in the set we have tested.

Because of the heavy labor of empirical testing, very few extensive explorations have been made; and the same is true of the validation of most other assumptions. Electronic computers reduce the labor greatly, but it would take a long time to explore the infinite variety of medical measurement data. Actually, research workers' confidence in the tests and estimates seems to depend largely on the fact that statisticians or textbooks have shown them how to perform the arithmetic; and statisticians' confidence in the techniques often seems rather analogous to some physicians' faith in uncontrolled clinical experience when evaluating drugs.

GAUSSIAN ASSUMPTIONS AND CLINICAL "NORMALITY." Perhaps a medical research worker feels justified in accepting at second hand the statisticians' faith when he feels unable to judge for himself; but this hardly justifies him in exceeding the statisticians in faith, especially in matters where he can obtain some direct evidence. For example, the Gaussian assumption perhaps often does little harm when we are comparing mean values; but this does not justify us in trusting it for individual measurements. So many frequency distributions of anatomic, physiologic, and biochemical readings are obviously non-Gaussian that it is surprising to find clinicians accepting the Gaussian curve—the "normal" (i.e., standard) curve in the mathematical sense—as a standard biologic phenomenon when they are assigning upper and lower "normal" limits in the clinical sense, and accepting the standard deviation, a mathematical convenience, as if it were a biologic standard.

In choosing standards of clinical "normality" it is much more reasonable to make no assumptions regarding the shape of the frequency distribution and to use, instead of multiples of the standard deviation, the easily comprehended and arithmetically simple method of percentiles.[6]

Questions regarding assumptions. Second-hand faith is not a sound basis for a rational attitude to statistics. Therefore, before doing any statistical arithmetic we ought to ask three questions:

A. Instead of doing this arithmetic, how could we find the information that we desire by randomization trials? In general, for significance tests the trials would be of the card shuffling type, for confidence limit estimates they would be of the disk sampling type; but for each particular test or estimate we ought to be as specific as possible regarding the procedure.

B. What are all the assumptions that underlie the arithmetic?

C. What is the risk that the arithmetic, based on these assumptions and applied to our particular data, will give us an answer

(significance verdict, confidence limit, or other estimate) that will lead us to a different course of action than would the answer obtained by prolonged randomization trials?

For the reasons indicated above, the reply to the third question is often vague; and I am beginning to wonder if we can ever feel confident that the risk of wrong action is negligible unless a method which avoids the assumptions would give us the same verdict as an assumption-cluttered method. That is why rank-order tests in which measurements, in ascending order, are replaced by ranks (1,2,3,etc.), have a strong appeal, apart from their intelligibility and their arithmetic simplicity. They are not quite as sensitive in detecting real differences as are *t* and F tests; but often a slight increase in sample size will compensate for this defect. Theoretical statisticians ought to be encouraged to invent a wide variety of rank-order tests, and significance tables to use with them.

V. Obeying the rules of the game. If we wish to play the game of statistical arithmetic we ought to obey the rules of the game. For example, let us suppose that we perform an experiment on a certain number of animals, test the result (e.g., by *t* or chi square) and find that it has not quite reached the chosen level of significance. If we repeat the experiment on some more animals, pool the data with the previous set, test again and accept the result if it is "significant," we are fooling ourselves and others. The probability tables of *t* and chi square say that, if we take *random* samples from the same population we shall meet such and such values (of *t* or chi square) in a certain percentage of trials. But the samples to which we applied our final test were not random; they were determined in part by what we found after the first experiment. Therefore, when there is no real (population) difference we shall find more than 5 per cent of differences "significant at the 5 per cent level." If we wish to do step-by-step testing, we must adopt another design, usually a "sequential" design, and that, also, has rules that we must obey.

VI. Disagreeable doubts. We ought not to dodge disagreeable doubts. For example, at the end of an experiment we say that the alternative causes of the result are "either chance (our randomization) or the factors under test"; but how do we know that our randomization was truly random? Random numbers, which we commonly use nowadays, are safer than any single card shuffling or disk sampling, for they have been extensively tested by comparing them with what would occur if card shuffling could be perfect; but for randomizing in a particular experiment we may have picked an area where there is some clustering or systematic sequence of digits. Again, in spite of every precaution in a double blind trial a leak of information may have occurred. All that we can say after any single experiment is that we believe the risks are trivial compared with the allowance that we make for purely random variation; and we must remember that, in Fisher's words, "an isolated record" is not an experimental proof.

VII. Limitations of confidence limits. When we meet, or make, confidence limit estimates we should know their limitations. If a consignment of screws or tables or raisins is sampled by a random method and in the sample Y per cent of the items are defective, we can find lower and upper confidence limits, X and Z per cent, and make a statement such as: "The proportion of defective items in this consignment may lie anywhere between X and Z per cent, but there is a probability of at least 95 per cent that it does not lie outside those limits."

If after a laboratory or clinical experiment the same kind of statement is made regarding percentage frequencies or mean differences or other measurements, we should change the wording after "but" into a form such as "*if* our sample *were* a strictly random sample of its population there *would be* a probability of at least 95 per cent that. . . ." In dealing with meas-

urements we should often add other "if" clauses, such as "if the frequency distribution of the population were strictly Gaussian."

In whatever detail we describe our laboratory animals or patients, we cannot safely consider them as strictly random samples of the populations so described. The great value of confidence limits, therefore, is that they reveal how little we know by showing us how little we would know, even if our samples were strictly random. The only way to learn something about the safety of our numerical or other findings is by more extensive exploration, i.e., repetition of the experiment under other conditions, in other places, and at other times, and by probing more deeply, to discover underlying mechanisms.

VIII. Is the technique really useful? This is a very effective question in our efforts to evaluate statistical methods—to break away from habit and tradition, and to avoid being mesmerized by methods of experiment design and analysis invented by some statistical mathematicians "who do most valuable work in the theoretical development of the subject, but who have no serious interest in the applications of statistical methods to happenings in the real world . . . [and] seem to imagine that they can design and analyze experiments on pigs one day and on pig iron the next without knowing anything about the personal pecularities of either animal."*

"Is it useful?" implies several questions such as "Does this technique (of design or analysis) tell us what we actually wish to know?" and "Is it reliable enough for our purpose?" If we cannot answer such questions, surely we ought not to employ the techniques.

IX. Avoiding the blind use of techniques. The thorough application of statistical thinking to the design, performance, and analysis of an investigation is an art in which even experienced practical statisticians make mistakes. *A fortiori*, even a senior research worker, if he has previously done nothing with statistical techniques except apply tests, is likely to go astray, even in apparently simple projects, unless he is willing to be guided in planning and conducting his investigation by someone (whether labeled "statistician" or not) who is truly able to guide him.

To be a safe guide a statistician must, as Bradford Hill has said, immerse himself in the particular project "up to his neck." Some statisticians, it is true, are willing, or are forced by financial or other pressures, to dip no more than a finger or two into projects in which they will be held responsible for analyses and inferences. Probably this is one reason why many investigators, administrators, and research-sponsoring agencies appear to think either that one or two fingers will suffice or that a statistician has an unlimited number of necks. Actually, there are not enough suitable persons to guide, in two or three projects per investigator, more than a small fraction of the investigators who are willing to be guided. Therefore, it might seem that we must continue for years to witness such pathetic events as the arrival at a statistician's office of a junior research worker or graduate student to have a test done because his research advisor fears that an editor, or the editor's statistical referee, or a thesis-review committee will frown upon a report that is lacking in tests. A more likely, and more fearful, alternative is that more research advisors will learn to do the tests themselves and show their disciples how to do them.

Such a depressing prophecy could, I think, be falsified if investigators would stick boldly by a belief to which we all pay lip service: the belief that a research worker can contribute valuable information if he will confine himself to efforts that are within his knowledge and skill, plan his work with much thought, perform it meticulously, record the observations in detail, criticize his results severely, and offer a modest—"it seems as if"—conclusion.

A report of such work often reveals ba-

*Finney, D. J.: Personal communication.

sically statistical thinking, and it is a pity that the author does not know how much he could be helped by more knowledge of the art; but this is no reason why he should sprinkle his report with sigmas, *t*'s, F's, P's and the like, when he has not planned and conducted his work so that these things will have a real meaning, and when he does not understand what they mean. Why should it not be permissible for him to state that he had not the knowledge, or adequate guidance, to design and conduct the research in such a way as make statistical tests and estimates meaningful?

Attitude to statisticians

If we developed a better-informed attitude to statistics we would develop a more realistic attitude to statisticians. For example, if we took our data to a statistician *after* an investigation we would choose one whose office would merit the title bestowed on the office of Professor Greenwood whose remarks were quoted at the beginning of this article—"The cold water department." We would vie with the statistician in the hunt for defects in our work, and would be suspicious of those statisticians who applied tests to such *post facto* data, unless they did so in order to reveal defects and limitations. If we reported any of their tests we would report, also, their precise interpretations. We would be suspicious of those statisticians who are willing to give us advice at the outset of our investigation and then, having had little or no contact with the work during its progress, perform analyses and give us unqualified positive answers at the end.

We would, of course, condemn those investigators who in their reports shelter themselves behind statisticians' skirts, or who, in order to win approval for a grant application, name a statistician as cooperator without first obtaining his permission and giving him time (usually several months) to cooperate in preparing the plan.

A hope for the future

The foregoing suggestions are presented in the hope that they will be supplemented by other writers, and will, by reducing the perversion of statistics, enable medical research workers to benefit from true statistical thinking.

References

1. Bronowski, J.: The Common Sense of Science, New York, 1959, Random House, Inc.
2. Cushny, A. R., and Peebles, A. R.: The Action of Optical Isomers. II. Hyoscines, J. Physiol. **32**:501-510, 1905.
3. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh and London, 1925, Oliver and Boyd.
4. Fisher, R. A.: The Design of Experiments, Edinburgh and London, 1935, Oliver and Boyd.
5. Greenwood, M.: What Is Wrong With the Medical Curriculum? Lancet **1**:1269-1270, 1932.
6. Herrera, L.: The Precision of Percentiles in Establishing Normal Limits in Medicine, J. Lab. & Clin. Med. **52**:34-42, 1958.
7. Hogben, L.: Chance and Choice by Cardpack and Chessboard, New York, 1950, Chanticleer Press, vol. 1.
8. Hogben, L.: Statistical Theory. The Relationship of Probability, Credibility and Error, London, 1957, Allen and Unwin.
9. Mainland, D.: Statistical Methods in Medical Research. I. Qualitative Statistics (Enumeration Data), Canad. J. Research, Sect. E, **26**:1-166, 1948.
10. Mainland, D.: Elementary Medical Statistics. The Principles of Quantitative Medicine, Philadelphia, 1952, W. B. Saunders Company.
11. Mainland, D., Herrera, L., and Sutcliffe, M. I.: Statistical Tables for Use With Binomial Samples—Contingency Tests, Confidence Limits, and Sample Size Estimates, New York, 1956, New York University Department of Medical Statistics.
12. "Student" (Gosset, W. S.): The Probable Error of a Mean, Biometrika **6**:1-25, 1908.
13. Wilson, E. B., Jr.: An Introduction to Scientific Research, New York, 1952, McGraw-Hill Book Company, Inc.

Symposium on the study of drugs in man

Part IV. Some social and cultural factors in American society conducive to medical research on human subjects

Because the role of medical research subject and the role of clinical investigator in the United States hold forth a series of instrumental, value-symbolic, prestige, and sociopsychological attractions and rewards, there are many persons in our society willing and able to undertake these roles, despite some of the strains they also entail. We suggest that the social and cultural factors which help to make the roles of investigator and subject practicable, tolerable, and rewarding in our society are not necessarily present in the same combination or to the same degree in other, present-day Continental European countries. Partly as a consequence, conducting medical research on human subjects seems to occur less frequently and involve more strain in those societies than in our own.

Renée C. Fox, Ph.D. *New York, N.Y.*
Barnard College, Columbia University

Precise statistics regarding the amount of human experimentation which is being conducted in present-day American medicine are hard to obtain. However, the general consensus on the part of persons currently writing about this form of medical research seems to be that in recent years the felt need for such experimentation on human subjects and its actual occurrence in our society have dramatically increased:

"The development of medicine, the safeguarding of health and some types of basic scientific advance all require human experimentation . . . . While prior experimentation in animals is absolutely necessary, when possible, the crucial study of new techniques and agents must be carried out in man . . . . Man as the essential final test site has come into adequate prominence only in recent decades. The current development of human biochemistry, human physiology and human pharmacology has made it plain that man is the 'animal of [illegible] here . . . ."[1]

"[illegible] there is every reason to believe that there has been a substantial increase in the

number of physicians who are engaged in more or less organized meddling with the private homeostases of the hospital patients of America . . . ."*

"The public interest in medical research, as evidenced in the mounting and spectacular support of private, voluntary, and government medical research of all types, clearly demonstrates current popular favor. Never have we witnessed such all-out willingness to conquer disease and to prevent illness, even to attempting the halt of the aging process. Acceptance has been active, through participation in anti-poliomyelitis vaccine trials, multiphasic screenings for cancer, tuberculosis, community election of fluoridation, and agreements to periodic check and control for cardiovascular disease. Institutionalized populations have been subjected to drug trials, nutrition experiments, metabolic regimens, and respiratory virus effects. Successful drives on the part of eye banks, organ and tissue banks, blood pools are further salutes to science . . . ."[15]

Various objective indicators that point toward the continually increasing amount of human experimentation in American medicine are suggested by these and other writers. For example, as Dr. J. Howard Means[20] reminds us, it is only in this century that we have had the emergence and significant development of a specialized role devoted to medical research on human subjects: the role of professional clinical investigator:

"For many years discovery and research were incidental to medical practice. The practitioners who staffed the hospital accomplished them in their stride. Toward the end of the first hospital century, however, what may be called the 'professional clinical investigator' made his appearance . . . . [The] professional clinical investigator . . . is a product largely of the present century . . . ."

Dr. Walsh McDermott has provided some data on the growing number of young doctors who engage at least temporarily in clinical investigation on the way toward certification for various kinds of specialized medical practice:

". . . [There] has been an amazing enlargement of the total pool of young people engaged at any one time in clinical investigation . . . . One index is the fact that one or two thousand non-member young people attend the meetings of the Society for Clinical Investigation . . . at Atlantic City each spring, Another index is the number of postdoctorate research fellowships awarded by the National Institutes of Health which now reach between 450 and 500 per year with a great predominance in the clinical field. The voluntary health organizations in tuberculosis, cancer, heart, multiple sclerosis and so on . . . each has its own well developed fellowship program."*

One of the factors contributing to the enlarged number of available clinical research positions currently occupied by American physicians, of course, is what has been referred to as the "mounting and spectacular" financial support of medical research by the American public. This, too, is a measure of the impressive amount of medical experimentation on human subjects now taking place in our society. For example, in President Eisenhower's Budget Message presented to Congress in January, 1960, the following statement was made about the expanding amount of Government money being allocated to clinical medical research:

". . . The Federal Government has expanded its public health programs and is actively seeking solutions to the Nation's health problems. Expenditures in the fiscal year 1961 are estimated to total $904 million, which is $53 million more than in 1960 and nearly three times the level five years earlier. The largest part of the increase is for medical research and the training of research workers through programs of the National Institutes of Health, for which the estimated expenditures of $390 million in 1961 will be four times as great as five years ago . . . ."

What is more, Government funds represent only part of the funds currently being invested in clinical medical research. Generous financial support also comes from universities and medical schools, industry, and

*McDermott, W.: A Consideration of the Present Ethics of Clinical Investigation, unpublished paper.

*McDermott, W.: A Consideration of the Present Ethics of Clinical Investigation, unpublished paper.

philanthropy. For example, the American Heart Association alone has allocated several million dollars for 1960-1961 to support a "far-reaching nationwide research program into diseases of the heart and blood vessels, including congenital heart defects":

". . . Allocations of almost $2 million in support of this research have been made by the American Heart Association's research committee for the 1960-1961 fiscal year, the association announced last week. These awards, the first part of the national program for 1960-1961, provide for 187 fellowships and lifetime investigatorships. They will be supplemented shortly by allocations of about $1.5 million as grants-in-aid, all from funds contributed to the 1959 Heart Fund campaign. . . ."[24]

Mention of the National Institutes of Health in the foregoing passage suggests another indication that the amount of medical research on human subjects in this society is mounting. For, in 1953, at the Clinical Center of the National Institutes of Health in Bethesda, Maryland, a 500 bed hospital unit for persons voluntarily undergoing various kinds of medical research was opened. This is a colossal version of the growing number of research wards specifically designed to carry out studies in patients which have been established in American hospitals in recent years.* In addition, a certain number of beds in every hospital affiliated with a medical school in the United States are given over to patients participating in research.

It is not only patients who serve as volunteer subjects for medical investigation. It has been estimated that as many as 20,000 Federal prisoners are participating as volunteers in medical experiments.[33] Men in the Armed Forces, persons of special religious or ideological conviction (such as Quakers, Mennonites, members of the Assemblies of God and Church of the Brethren), scientists, physicians, nurses, technical aides, and students are among the groups from which it is known that a significant number of persons enter into the role of volunteer research subject.

Indeed, even the casual patient seen by the doctor in his office or at home may now be a quasi-volunteer in a quasi-experiment. All diagnosis and treatment involve some element of experiment. "If it comes to that," Sir Geoffrey Jefferson[11] has said, "all medical treatment is also experimental. . . . The prescription even of rest in bed for two or three weeks, or of a bottle of cough mixture, are experiments, the results of which deserve closer observation and quantitative analysis than they get." This element of experimentation has been enlarged by the rapidity with which new medical techniques, especially new drugs, move from the laboratory to the doctor's office. In the United States, at present rates of development, about 400 "new" drugs are offered by pharmaceutical manufacturers to practicing physicians every year. The patient who accepts the new drug which the doctor says he would like to "try out" is in some measure a volunteer in the widespread experiment to test its efficacy and side effects.

Furthermore, as already mentioned, since World War II, we have seen and participated by the thousands in a new, mass-organized kind of research on human beings. The most notable example of this sort of large-scale research was the trials with Salk poliomyelitis vaccine recently conducted on a nationwide basis.

The purpose of this paper is to explore some of the reasons for which a continually increasing amount of medical research on human subjects seems to be taking place in American society. It is our basic hypothesis that certain social and cultural factors in our society which support and surround clinical medical research not only create many situations in which persons are needed and requested by physicians to act

* One of the very earliest of such units was the Metabolic Ward at Bellevue Hospital in New York City, founded in 1913 by the late Professor Graham Lusk and Dr. Eugene F. Du Bois, and supported by the Russell Sage Institute of Pathology. A second is the Mallinckrodt Research Ward (Ward 4) of the Massachusetts General Hospital for endocrinologic and metabolic research, founded in 1925.

as research subjects, but also help to positively motivate a significant number of individuals to undertake this role. Implicit in our hypothesis is a second, comparative assumption: that this constellation of social and cultural factors is not present in the same way or to the same degree in other contemporary Western European societies, and that, partly as a consequence, there is significantly less likelihood that persons in those societies will be asked by physicians to participate as subjects for medical research, or will desire and agree to do so.*

Availability of funds and equipment for clinical medical research in the United States

Perhaps the factors most widely recognized and frequently cited as conducive to extensive medical research in American society (and hence, indirectly, to the participation of many persons as medical research subjects) are the ample funds and technical facilities available to physicians and medical scientists for the conduct of such experimentation. Numerous European physicians, for example, have attributed the impressive amount and vigor of medical research in the United States to the fact that "this country enjoys financial sources which are infinitely superior to those of Europe."[4†] The availability and provision of such resources for clinical medical research, of course, are fundamentally connected with the relative economic affluence of our society. But, as a young, European-born research physician has recently pointed out, national prosperity per se is not the sole and perhaps not the primary reason for the great amount of excellent medical research being conducted in the United States today. The fact that "this country is wealthy and [that] American laboratories receive many funds from different sources," is "indisputable," he writes. "But Western Europe is far from being poor."[4]

"No, it is not only a question of money," writes the special correspondent in Rome for the Belgian newspaper *La Libre Belgique*, in a recent article on why so many young Italian scientists are leaving their country and coming to the United States to pursue their research:

> ". . . It is true that the most simple scientific laboratory today costs several million francs, and that for certain experiments, even larger funds are necessary; but what Italian scientists complain about—particulary physicians—is that in Italy today, the public and the Government are not sufficiently aware of the importance of scientific research in the technical and industrial revolution. Italian scientists work in an atmosphere of indifference; they feel abandoned.
>
> "To be sure, both the Government and private industry in Italy give certain large sums for scientific research each year, and now and then some really important things like the synchroton of Frascati near Rome are realized; but these constitute exceptions.
>
> "The Italian press writes that it is not surprised that the youngest or the most famous scientists leave Italy to establish themselves in the United States or in countries where they can deepen their knowledge and devote themselves to research in a favorable atmosphere.
>
> "Italians have recently learned, with bitterness, that one more famous physician is leaving the country for the United States: Professor Giuseppe Occhialini, Director of the Institute of Physics of the University of Milan, known all over the world for his studies in the domain of cosmic rays. This news made even more of an impression on Italian opinion due to the fact that the Nobel Prize has just been awarded to Professor Segre, another Italian scientist who emigrated to the United States several years ago and became an American citizen . . . ."[34]

"The American public is devoted to med-

*This assumption is not only based on some of the published literature I shall cite in the course of this paper, but also on some of the observations I made and interviews I conducted in various French, Swiss, and Belgian university medical centers. For, from June to September of 1959, with the help of a stipend from the Council for Research in the Social Sciences of Columbia University, I began the exploratory phase of an inquiry into problems of clinical medical research in a Continental European society. The particular site of my long-range study will probably be Belgium, where I shall continue my research this summer, with the assistance of a Commission for Relief in Belgium Special Fellowship of the Belgium American Educational Foundation.

†Translations from the French are by the author.

ical research," Dr. John Z. Bowers[2] recently commented. Or as a Swiss physician* once remarked to us, Americans have "un sens civique scientifique." What these various physicians seem to be independently observing is the existence in American society of an unusually widespread, strongly felt belief in the moral and practical importance of medical research and a sense of individual and collective responsibility about supporting it, such as is reflected in the following passages:

"The 'Health for Peace Act' . . . was passed on 20 May (1959) by a vote of 63 to 17. The bill . . . provides for the establishment of a National Institute for International Medical Research . . . . [It] also authorizes the appropriation for the program of $50 million annually . . . . Some of the purposes of . . . [the] Resolution are as follows:

"1) To encourage and support the planning of essential research into disease, disease prevention, and impairments in man on a worldwide basis.

"2) To encourage and support, in part through direct financial grants and loans of equipment, scientific research projects on diseases and physical disability that are being conducted in institutions abroad . . . .

"The bill has widespread support from the press and the public . . . ."[30]

"William Black, president of the Chock Full O'Nuts Corporation, yesterday gave $5,000,000 to Columbia University toward the construction of a medical research building . . . . The research building, an eighteen-story structure will be erected . . . on the campus of the College of Physicians and Surgeons. One floor will be used for research projects of the Parkinson's Disease Foundation which Mr. Black founded in 1957 . . . . The building will be the largest voluntary medical research building in the country.

"In presenting the gift, Mr. Black said: 'It is my heartfelt hope that this investment in scientific research will aid in solving the medical mystery known as Parkinson's disease, and other unsolved afflictions of mankind. If this can be achieved during my years on this earth, then my dream of helping a lifelong friend who is a Parkinson patient, will have come true.'

"Mr. Black said he derived particular satisfaction in being able to make the gift because one of his problems as a Columbia student was 'the basic one of earning the next semester's expenses while getting enough to eat during the current semester.' "[23]

"Edward Mallinckrodt, Jr., native of St. Louis, manufacturing chemist, graduate of Harvard College . . . Overseer of Harvard . . . has taken a deep interest in scientific research, both in basic sciences . . . and in medical research and education during his whole career. All along . . . he has been the generous and discriminating patron of scientific research and education . . . . In addition to his successful leadership in a vital industry, his life has been devoted to the promotion of what he has regarded as the most promising activities in science and its applications to human welfare . . . .

"It was in 1945 that he first contributed directly to the operating costs of Ward 4 [the research ward of the Massachusetts General Hospital]. In that year he began supporting one of the ward's ten beds. This was but a trickle compared with what was to follow. From then on his gifts steadily mounted, so much so that on August 20, 1948, the Trustees voted that Ward 4 be named for [him] . . . that it be known as the Mallinckrodt Ward . . . ."[20]

". . . For progress in medicine," writes Dr. Means[20] "we must have sick people (and also, for control, well ones) studied both at the bedside and in basic-science laboratories; furthermore . . . the results of such studies must be reconciled, correlated and fully integrated in order to derive concepts of the total nature of the patient and his illness. The patient is as necessary to medical research as to medical education—that is to say, he is indispensable. It is the picture of disease as seen in the patient that creates problems for investigators to solve . . . .

"We have hardly ever had any difficulty in inducing patients we wished to study to enter the ward . . . . The knowledge that they are participating in the progress of medicine is gratifying to them. Indeed, patients no less than investigators have shown both loyalty and devotion to the cause of research . . . ."

*Personal communication.

The senators, the sector of the lay press and of the public, the businessmen, the research physicians, and the patients cited in these passages all manifest a desire to contribute generously to medical research. Their motives for doing so may vary: political incentives; the sense of noblesse oblige of an upper-class businessman; the triumphant gratitude of a modern Horatio Alger; the desire to help an afflicted friend; the hope that something can be learned about one's own illness, and so on. The diversity of motivation notwithstanding, a commonly held set of beliefs runs through all these statements and actions on behalf of medical science: Disease is an evil that afflicts mankind. As much as possible ought to be done to understand disease better in order to prevent, ameliorate, cure it. One of the most basic, important ways to achieve this is through medical research—research which must be conducted on man, as well as on animals and in test tubes. It is the moral obligation of every individual, and of our society as a whole, to support medical research, both here and abroad. In this domain, as elsewhere, "virtue is its own reward." But, in addition, those who give lavishly, sacrificially, creatively, to the support of medical research, are deserving of special commendation and recognition.

Factors that motivate American physicians to do clinical research and offset strains of experimenting on human subjects

Even the fact that a significant number of American physicians are sufficiently convinced that clinical medical research is important and justified to conduct experiments on human subjects cannot be taken for granted. For the role of clinical investigator entails heavy moral responsibility and considerable strain.*

Human experimentation, like all research, is to some extent a voyage into the unknown. As such, it involves inevitable uncertainty and possible harm to the subjects of the experiments undertaken. It is this uncertainty and possible harm which create strains for the clinical investigator who has the dual responsibility, on the one hand, of protecting and furthering the welfare of his patients and subjects, and, on the other, of advancing general medical knowledge.

". . . When the clinical researcher goes to his wards his purpose is not to recognize the known, but to face the unknown . . . . Experimental research upon disease may very readily come into conflict with full solicitude for the sick. When such conflict threatens, as it not infrequently does, it is unquestionably right that research should give way unhesitatingly . . . . No worker can reasonably expect to be relieved of full responsibility in the care of any patient remaining in his charge; but, on the other hand, it is to be realized that no investigator can be successful who allows, or is forced by circumstances to allow, solicitude for his patients to preoccupy his mind . . . .

". . . The purpose of such experimentation is usually to elicit information of value to the science, and thus to benefit patients in general; it often—but by no means always—elicits information of immediate benefit to the actual patient.

"Manifestly no test is justifiable which adversely affects the subject of it. This is a matter which deserves and requires adequate safeguards. The most important safeguard is a proper sense of responsibility among those concerned . . . . No test other than those of a class generally regarded as producing at the most a temporary discomfort should be undertaken without full previous discussion, and without reasonable grounds to believe that it is in the patient's own immediate interest. The touchstone may often be that all parties concerned are willing to submit to the same test. It goes without saying that the fully informed patient should be a consenting party."[18]

In short, the clinical investigator is continually faced with a considerable amount of moral ambiguity, and with some moral conflict over the justifiability of the experiments he is conducting on human subjects. Various attempts have been made to set forth basic rules or principles to govern ex-

*See Fox,[8] especially pp. 26-64, for a more extensive, concretely detailed account of the problems and stresses experienced by a particular group of clinical investigators who were studied by the author.

perimentation in man. The principles most often cited as a guide are those of the so-called Nuremberg Code: ten rules defining ethical experiments on human subjects which were laid down at the Nuremberg military trials of Nazi medical war crimes.[25] But the basic rules do not tidily resolve the strains confronting the clinical investigator and may even engender new questions and difficulties. For example, it has been stated that it is "absolutely essential" that persons who act as subjects be fully enough informed about the experiment they are asked to undergo by the physician-investigator to enable them to make an "understanding," "enlightened," and hence, truly "voluntary" decision to do so.* However, in the words of a medical investigator,[10] "one has only to think of present-day specialization in medicine . . . with its increased technicalities . . . to realize that no matter how conscientious or detailed the investigator may be in explaining a procedure, the subject is "frequently not able to grasp all [its] implications so far as his health is concerned." For that matter, given the inherent uncertainties connected with trying a new procedure or drug on a human subject, the degree of physiologic variation which normally exists among individuals, and the complicated or precarious state of health of many of the patients who serve as subjects, the investigators are often in a position where they can only roughly predict how much danger, suffering, or inconvenience a proposed experiment will involve for their subjects, or whether its ultimate contribution to the advancement of science, health, and human welfare will be sufficient to justify such risks and discomforts:

". . . How is the investgator to draw a practical line in the prior information to be given his patient, between 'reasonably to be expected' and possible hazards, when these often will be quite unknown in first experiments? . . . Cardiac catheterization, whose wide usefulness has been recognized by a Nobel Prize, could, in its early days when its value was not known, have been challenged on serious grounds as jeopardizing the immediate subject's life. Subsequently this has indeed been proved at times to be the case. At present, it is widely recognized that the demonstrated value of the technique outweighs the risk. Ladimer has described in chilling detail the probable fate in a court of law of the conscientious but bold investigator who takes such risks and has his failures early. In most cases, neither true risk nor benefit can be known early and therefore they cannot be adequately described."[1]

One of the major findings which emerged from our own study of a group of American clinical investigators was that these physicians often felt quite disturbed over the inadequacy or uncertainty of their knowledge, and the difficulties they experienced in trying to reconcile their clinical responsibilities with their responsibilities as investigators. And yet, for all its problems and stresses, they chose to work as clinical investigators, found much that they considered important and gratifying in this work (and to this day continue to do comparable medical research). The question we wish to raise here is: Given the strains associated with experimentation on human subjects, why are there so many American physicians who engage in this type of research (temporarily or permanently, on a part-time or full-time basis); and what factors are present in their research situation which compensate for these strains, and help to minimize them?

To begin with, we return to the observation already made that a significantly large number of physicians in our society seem to share the conviction that this kind of research is socially necessary and desirable because it contributes to scientific and medical knowledge in ways that cannot be obtained through experimentation confined to animals. Thus, many American physicians consider it their professional duty to see medical science advanced in this way, by undertaking some clinical research themselves, by supporting those of their

*See Nuremberg Rule No. 1.

colleagues who are engaged in this kind of investigation, or in both these ways:

"It is clearly evident . . . that human experimentation is essential for the welfare of the race, for in medical research lies 'a common benefit not obtainable by other means.' The development of medicine, the safeguarding of health and some types of basic scientific advance all require human experimentation . . . ."[1]

". . . Experimentation on human beings, including the sick, must be performed if we are to advance our conquest of disease. There can be no question of the value of this type of investigation for the improvement of the care of the sick . . . ."[10]

". . . The care of the individual patient remains a prime duty of the medical profession, but medicine in its modern meaning involves social, political, ethical, economic and educational responsibilities as well. In all of these areas . . . research is necessary to progress. Practice, education and research must be sweetly blended in order that progress can be made as effectively as possible toward the ultimate human good . . . .

"The research performed in Ward 4 and its adjacent laboratories has been of the clinical type . . . . A place like Ward 4 provides the newest that is known in the care of the sick while it advances the boundaries of knowledge in the field concerned . . . . May [it] continue its good service to the cause of medical research . . . ."[20]

This degree of commitment to the idea that medical research on human subjects is scientifically essential and morally and socially good is certainly not true of all American physicians. As Shimkin (a medical investigator at the University of California) has pointed out:

". . . Despite the demonstrated value of medical research in terms of saving life, relieving pain, and achieving other goals considered worthy, the use of human beings for experimental purposes often encounters vigorous opposition. Proposal of such investigations, even to groups trained in scientific disciplines, may result in outright rejection or in the suggestion that animal experiments that a priori can be seen to be inadequate for the solution of the problem be substituted . . . ."[31]

It is the opinion of a number of European physicians, however, that by and large a positive attitude toward clinical medical research is more characteristic of American physicians than of physicians in Continental Europe. They suggest that the conflict between conducting experiments on human subjects and living up to the responsibility to promote the welfare of persons in their care is likely to be experienced by American physicians in a form that is less acute and research-incapacitating, than that felt by many European physicians. These writers indicate that the belief of American physicians in the practical and ethical importance of clinical research seems to be strong enough not only to reduce this conflict in such a way as to favor research, but also to overcome to a much greater extent than in Europe the sort of individualism and professional rivalry that deter necessary and fruitful collaboration between medical investigators in different fields, departments, and institutions.

". . . More and more the tendency [in medicine] is to the laboratory . . . to the systematic biological investigation of patients of those in good health . . . . In the United States, Professors of Biochemistry, of Physiology, of Anato-Pathology are named Clinical Professors . . . .

"In France, the imminence of unavoidable changes hardens the oppositions. In the universities, scientists and clinicians confront one another . . . .

"It is precisely the clinic which is at the center of the conflict of doctrine. For a century experimental science has been engaged in an assault on illness . . . . All the basic sciences . . . have been incorporated into biology . . . . As long as they operate in the laboratory, no doctrinal problem arises. As soon as they are applied to man, the difficulties begin, because here they enter into play with the clinic . . . .

"Between the two [World] Wars . . . the development of applied physiology was impossible, and when my colleague . . . and friend, André Cournand wished to undertake research on respiratory physiology applied to man, he had to leave his country, because as he said to me, he 'felt that he would not be able to carry his ideas to their end point [here].' . . . After thirty years of tenacious

work, he founded a discipline and achieved glory . . . .*

"Claude Bernard did not wish to create an air-tight division within medicine between experimental medicine on the one hand, and the clinic on the other. He wished to see them co-penetrate. He did not want the clinician to approach problems of illness in a fashion that is exclusively descriptive; but rather advocated that he turn the eyes of an experimenter upon these problems and carry out the essential task of searching out in all phenomena the relations between cause and effect . . . .

". . . To become a clinican for life . . . is to be a savant, inclined as a biologist toward man and his suffering, looking closely through incessant research for ways of understanding and curing it, without ever ceasing to be close to his spirit and attentive to his heart!"[12]

"It is the mentality prevalent in American research centers which makes the work stimulating and profitable, above all by the fact of effort in common. Americans are perfectly logical in this point of view: the domain of the unknown in biology is immense and from [recognition of this] derives their concern to accept every suggestion capable of advancing knowledge, no matter where it comes from . . . . [As a result] the possibility of a continuous exchange of ideas and information in the heart of the scientific world increases tenfold the efficacy of the researcher . . . .

"I don't know if Americans have ever formulated their scientific attitude in precisely these terms, but one must admire their realism in this matter . . . . Their behavior [is] much more reasonable than ours, as much as we would like to think of ourselves as disciples of Descartes! Isn't the European biologist usually very isolated, and isn't this isolation above all the result of a touchy individualism and a misplaced amour propre?

"Our handicap it seems to me is due above all to lack of collaboration . . . . I am convinced that in Europe we have to make a great collaborative effort, and I hope that we will have the courage to do so."[4]

The prevalence of teamwork in American medicine, so frequently commented upon by European observers, not only facilitates research in an intellectual sense. It also serves the more latent, sociopsychological function of making it easier for clinical investigators to cope with some of the strains that accompany their research on human subjects. As Shimkin has said, ". . . research on human beings is too hazardous and implies too many responsibilities to be undertaken by lone investigators."[4] But when such research is conducted as a group effort, the investigators are able to help one another decide whether or not a contemplated experiment is morally permissible and desirable, and can also give one another support in the face of difficulties that may arise once they have jointly launched an experiment.

These functions of informal relations between members of a research team have been observed in a group of clinical investigators working with chronically ill research subjects.[8] The unity of this small group of physicians made it possible for them to exchange opinions and feelings about the common problems involved in conducting their experiments. In various informal settings and intimate meetings, the members of the group expressed a good deal of tension, moral disquietude, and frustration over their problems. The effect of sharing these feelings with colleagues who faced the same problems and reacted in the same way was to give all of them, as one member put it, "a lift" which they needed and welcomed. These investigators considered their discussions "stimulating . . . helpful . . . and valuable" because they felt that there emerged from these exchanges a policy for their experiments which was not only scientifically, but also morally, sound.

Furthermore, in many of the teaching and research hospitals and centers conducting clinical investigation in the United States, there exists "formal [as well as] informal machinery . . . for impartial group

*Dr. André F. Cournand migrated to the United States in 1930. In 1956, he (and two other medical researchers) won the Nobel Prize for perfecting cardiac catheterization, a method by which physicians can explore the interior of the human heart. He is Professor of Medicine at Columbia University and has recently been named the first encumbent of the Westchester Heart Association Professorship of Cardiovascular Research, which was established this year at Columbia's College of Physicians and Surgeons.

consideration of proposed research":

". . . Research committees, pharmacy committees, and other methods are provided for review of proposed clinical trials and investigations of other types. These groups look into purpose, theory or basis for the proposal, prior laboratory and animal analysis, reports on related studies, suggested control measures, evaluative technics and precautions for safety of the subjects . . . . At the Clinical Center of the National Institutes of Health, for instance, projects involving deviation from accepted medical practice or unusual hazard are presented in writing to a Clinical Research Committee. Consent is obtained from subjects and final approval from the Center's Medical Board and the Director of the National Institutes of Health . . . ."[14]

Along with the formal and informal relations of clinical investigators with each other and fellow physicians, certain aspects of their relations with the persons who act as their subjects facilitate their research.

In various ways American research physicians (whom we have observed or whose works we have read), seem to treat the individuals on whom they experiment as personal associates or quasi-colleagues—in the words of one physician, "as a virtual member of the research team."[7,8,20] Physicians usually tell subjects a good deal about the experiments in which they participate and, if the research subject is a patient, about the bearing the experiment he is undergoing may have upon his illness.

Clinical investigators also give special recognition to some of the persons who act as their subjects. "We celebrate our patients" was how one such investigator once described the way he and his colleagues treated their volunteer research subjects in rounds, conferences, technical medical publications, and even in releases to the lay press. Thus, in rounds and conferences in which medical investigators present their patients and their research to other physicians they often express their indebtedness and admiration for the part the patients have voluntarily played in the research:

"This is Leo Angelico . . . . Leo has been assaying ACTH for us for three years now. And we've gotten some wonderful baseline studies with his help. He's been written up in many of our papers . . . ."[8]

Or, again, medical investigators speak out in letters to their patient-volunteers:

". . . You will be interested in knowing that the results from the big experiment in which you were involved are of greatest interest not only to us, but also to many scientists who work on the new steroids in Switzerland and elsewhere . . . . You are now quite a famous person . . . . The article you appeared in was a teaching paper and has proved to be of considerable value to a large number of practicing physicians."*

Finally, in the prepared stories about their research activities which medical investigators sometimes release to the daily newspapers and weekly newsmagazines, and in the interviews they grant to science reporters, prestige is awarded to individual patient-volunteers:

"SURVIVES AFTER RARE OPERATION: Wayne Williams is congratulated by Dr. Herbert Norton on his ability to walk after having been bedridden five years . . . . Dr. Norton said that Wayne's case was the first time in medical history that a faulty heart valve had been restored through surgery . . . ."[8]

"Before the days of miracle drugs a man could not have lived more than a few weeks after surgical removal of his adrenals . . . . Last week the amphitheatre at —— Hospital was crowded with standees as Dr. John Thomas described cases in which patients have lived as long as nine months . . . and are still going strong . . . . [One patient] Walter Cousins, 32, had been given six months to live . . . . He had the operation done months ago, responded so well that he got a job as a night orderly at the Hospital . . . ."[8]

In addition, clinical investigators often give their subjects what one physician has termed "red carpet treatment." They extend special privileges and considerations to subjects which are not accorded the "usual"

*See also Means,[20] chapter V, "Charles Martell Shows the Way," for the extended glorification of a patient-volunteer.

hospital patient, such as free room and board in the hospital, free medical services, free supplies of new, scarce drugs, especially attractive hospital accommodations, and so on.

The manifest functions of the special personal and privileged ways in which clinical investigators treat the persons who act as their subjects, and of the ways in which they deal with them as if they were professional collaborators, are obvious.

By fully informing their subjects about the experiments in which they participate, of course, physicians are meeting the ethical and legal requirement that they obtain "the voluntary consent of the human subject," and that before they accept his "affirmative decision" they make "known to him the nature, duration and purpose of the experiment; the method and means by which it is conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiments."* Reinforcing the moral reasons for which physicians give subjects a detailed explanation of the experiments in which they participate is a more pragmatic one. It is their impression that this increases their motivation to act as research subjects and makes them more cooperative about the demands and restrictions the studies impose on them. Thus, to some extent, clinical investigators provide research subjects with information about experiments in order to secure their optimal compliance.

The same thing might be said about some of the ways in which clinical investigators treat their subjects as valued colleagues and privileged friends.

In addition, there are certain more latent functions that these informal relations between medical investigators and their research subjects seem to serve. "Thank you for suffering so stoically," a research physician wrote to one of his patient-subjects after he had been discharged from the hospital. This seems to be one of the primary things the clinical investigators we observed tried to convey to the patients who acted as their subjects through the behavior described. The intimate and extra things they shared with their subjects enabled them to show their personal and professional concern over the "suffering" to which research as well as illness subjected patients. It also seemed to have given these physicians some feeling that they were compensating patients for their suffering, or at least, that they were doing something to help counterbalance it. Thus, one of the implicit functions the special ways they treated patient-subjects seems to have served for this group of clinical investigators is that it helped to relieve them of some of the anxiety and guilt they felt about subjecting their patients to the strictures and hazards of experimentation.

To a degree, the personal and colleague-like intimacy and equality that tend to develop between clinical investigators and their subjects is influenced and facilitated by what would seem to be one of the general characteristics of physician-patient relationships in our society. Comments by European physicians sensitize us to the fact that, as a whole, American physicians are probably more inclined to give their patients detailed information about their illnesses—its diagnosis, treatment, and prognosis—than many of their European colleagues. A less egalitarian, more guarded, paternalistic conception of the physician-patient relationship seems to prevail in many parts of Europe. In this type of relationship the physician tries to protect his patient and maintain a certain degree of professional dignity and distance by cleaving to a very strict definition of "professional secrecy" ("Le secret professionel"):

". . . . One of the most frequent complaints of patients in [England]," writes a British physician,[19] "and one that reflects a certain difference of practice between this country and North America is the reticence on the part of doctors to discuss with them the medical details of their case . . . ."

*Nuremberg Rule No. 1.

"Professional secrecy has been the cornerstone on which the medical ethic is built," asserts Professor Pasteur Vallery-Radot[26] of Paris. "Vis à vis the patient the physician is held to the secret when he has discovered a serious disorder with a grave prognosis. In certain countries, it is considered a duty to tell the patient the unequivocal truth, no matter how cruel it is. In France, our conception differs: above all, we are concerned about the moral distress into which we can throw the patient. Our feeling leads us to give hope even when the situation is desperate. We avoid the brutality of confession.

"Medical secrecy vis à vis the public is imperative if one wishes to maintain the dignity of the profession . . . . In our opinion, even the most benign affliction should be divulged in confidence to third parties, even if they are also physicians . . . ."*

The tendency of American physicians in general, and of clinical investigators in particular, to communicate medical information fully to their patients and subjects is related to another phenomenon often commented upon by European observers: the fact that science as a whole, but above all, medical science, is "front-page news" in our society. Events and developments in medical research and practice are reported with frequency, prominence, and in great detail to the lay public by American newspapers and magazines, and by other media of mass communications as well.† A recent study of the science and medical news reading behavior and attitudes of over 1,900 American adults selected to represent a cross-section of the public revealed that studies of medical progress attract more attention from readers than almost any other science items, and that "the most latent desire for expanded news coverage existed for news about medicine and health." It was first on the "wants more" list with 42 per cent of all respondents.*[13]

To some extent, the tendency of American clinical investigators to impart a significant amount of medical knowledge to their subjects is a response to the fact that the persons who act as their subjects usually already possess a good deal of mass media–communicated medical information, and exhibit what seems to be a widespread American desire to learn even more. In a sense, then, the fact that the mass media convey medical knowledge to the public and increase their eagerness to acquire it, eases the work of clinical investigators. It provides them with another inducement and justification for telling their subjects a good deal about the experiments in which they take part. In turn, as we have already indicated, this semi-professional way of communicating with their human subjects helps investigators cope with the strain that conducting research upon them involves.

To summarize our discussion so far—We have suggested that a number of sociocultural factors present in American society not only make it possible for physicians to engage in clinical medical research on human subjects, but to a degree encourage such research. These factors include: a considerable amount of knowledge about medical research on the part of the American public, who also exhibit a highly developed interest and belief in such research and sense of responsibility about supporting it; strong intellectual, practical, and moral

*As this statement suggests, carried to its logical extreme, the conception of professional secrecy, based as it is on the idea of an exclusive "colloquium" between the individual physician and the individual patient, debars, or at least curtails, sharing information about a patient and his illness even with fellow physicians, or with social or government agencies that might have need of certain medical data. And indeed, up until the present day in France there has been difficulty in getting physicians to communicate information concerning their patients to Social Security, to patients' employers, etc., or sometimes to register the cause of patients' death with the appropriate public agency. This makes it far less likely than is true in our society that medical information and news will be conveyed to the public via mass media of communication.

†The task of transmitting scientific and medical news to the public is such an important and highly developed one in our society that the role of science writer now exists. A group of professional journalists who specialize in this kind of reporting have formed the National Association of Science Writers. To this writer's knowledge, this is a phenomenon especially characteristic of American society.

*This is a report of a cooperative study involving the National Association of Science Writers, the Rockefeller Foundation, New York University, and conducted by the Survey Research Center of the University of Michigan Institute for Social Research.

commitment to clinical medical research by a significant sector of the American medical profession; and the establishment by clinical investigators of relationships with medical colleagues and subjects which technically and sociopsychologically facilitate the carrying out of this type of research. These factors not only reduce some of the moral strain that experimenting on human subjects entails for research physicians, but also positively impel physicians to engage in some clinical research. For the sociocultural factors designated contribute to the fact that there are many clinical research positions with reasonably good salaries available in our society; that engaging in such research, even temporarily, is in certain respects professionally useful, prestigious, and rewarding for many physicians; and that their relations with colleagues and patients in the capacity of clinical investigators offer them personal as well as professional gratifications:

"[One of the] major implications of the raising of standards required for specialty practice [is] . . . the propulsion of a group of young men into the research field for a few years at a time—men who are principally dedicated to meeting the five-year specialty board requirements . . . .

"Irrespective of their motives, it is clear that [a large] group of young people are under considerable inducement to enter the clinical research field. For the many established clinical investigators frequently have more openings for fellows than can be filled at any one time from the available supply. In certain instances, to put it crudely, the situation is one in which the established investigators own the machines and have the money to hire the young people to work at the machines. Moreover, in inducing the young to have a whirl in clinical research, the established investigator without even speaking a word may have on his side all the subtle persuasiveness of his obvious success . . . ."*

". . . Scientific research has been the dominant theme in our medical schools since World War II. Research ability is essential for a faculty appointment in a majority of the schools. The pressure for research productivity permeates the activities of our faculties . . . ."[2]

". . . I made some of the finest and firmest friendships of my life [in the Metabolic Research Group]. It also provided a wonderful atmosphere for learning. My associates were all of high calibre, and I was tremendously stimulated by them . . . . And there was also pleasure . . . even inspiration in coming to know some of the patients so well . . . ."[8]

Factors that motivate persons in American society to play the role of volunteer medical research subject and that reduce its attendant strains

The positive inclination of numerous American physicians to engage in clinical research would be of little consequence, of course, were it not for the fact that there are many persons in our society willing to act as research subjects. As we have seen, most experiments involve some degree of discomfort and risk which the medical investigator is morally and legally obliged to make known to the prospective subject of an experiment in the course of obtaining his "voluntary consent" to undergo it. Given the inconveniences and hazards that experimentation may entail and the fact that acting as a research subject is a matter of personal choice, we may well ask: why do so many persons in our society voluntarily undertake this role? What are some of the factors that induce them to do so?

To begin with, just as conducting research on human subjects has certain instrumental functions for the physician (such as advancing medical knowledge in ways that could not be accomplished solely by experimenting on animals; earning a living; furthering one's medical career; and gaining public as well as professional recognition), so playing the role of volunteer research subject may serve as a convenient and necessary instrument by which certain individuals can achieve concrete goals they want to or are compelled to reach.

For example, we know that many pa-

*McDermott, W.: A Consideration of the Present Ethics of Clinical Investigation, unpublished paper.

tients serve as subjects, and that by volunteering to do so they may attain a variety of instrumental benefits. In some cases there is the possibility that new knowledge, techniques, or medicaments relevant to their maladies may result from the experiments in which they participate. Besides medical aid in this form, as we have already pointed out, patients who act as research subjects may be given free hospitalization and care, or access to otherwise rare or prohibitively expensive modes of treatment. For some patients, hospitalization as a research subject may provide a solution to a lonely or difficult home situation. The following three cases illustrate these instrumental functions:

". . . Margaret S., a widow of 54 . . . had begun to feel weak and run-down ten or twelve years before entry [into Ward 4, the research ward of the Massachusetts General Hospital] . . . . She came to Dr. Forbes at the MGH, who recognized that she had the symptom picture of classic Addison's disease . . . . Dr. Forbes at once appreciated that Margaret S. would give Dr. M. M. Pechet . . . an admirable chance to pursue his study of the relation between molecular configurations of steroid hormones and their physiologic actions on people . . . . Actually, the studies caused only temporary and slight inconvenience, and life in the ward itself she enjoyed, finding it preferable to her previously lonely existence in a lodging by herself."[20]

"Since 1950, this patient has been admitted every year to the Metabolic Ward [of a New England Hospital] as a volunteer . . . . a well-developed, well-nourished, healthy-appearing, young-looking, middle-aged male who shows no abnormalities other than paraplegia of the lower extremities and flaccid paralysis of the left arm . . . . On the ward, he stays in a wheel chair during the day, and requires the help of an orderly to be put to bed at night and in his wheel chair in the morning. He is pleasant and seems to be well-adjusted. He has found a fairly satisfactory solution to his problem by serving as a permanent volunteer for metabolic studies . . . ."[8]

"Mr. D. suffered from ill-health from 1922 on, which was finally diagnosed as Addison's disease in 1931, when he had a series of crises. He was treated with subcutaneous adrenaline, 6 injections a day, for a few years. From 1935 on he took Eschatin [adrenocortical extract] twice daily at a cost of $60 a week. Mr. D. reports, 'This took every cent I could lay my hands on.' In 1948 he was invited to volunteer for experiments with cortisone, which was to be supplied to him free. In addition, he was to be paid all transportation costs and $10. a day while in the hospital. After one such stay he wrote to the medical investigator: 'I want to thank you and Dr. T. for having me . . . for the recent tests. It was a good experience for me and the financial arrangement was most helpful, this being the first real hard cash I've been able to lay my hands on in some time. Do hope you will find an opportunity to use me again . . . .' "*

Another significantly large group of persons in American society who derive instrumental rewards from volunteering as research subjects are civil prisoners. "During World War II both Federal and State prisoners made important contributions to malaria studies, the use of blood plasma, plasma fractions and plasma substitutes, and trials of various new drugs. In most prisons, more volunteers were available than were needed."[1] The rewards given to prisoner volunteers for their service "vary all the way from gifts of tobacco to a full pardon."[1] Although there is some attempt not to "make representations to a prisoner concerning the extent and types of reward which may accrue as a result of his service as a subject in a medical experiment,"[9] in many instances terms are explicitly stated beforehand. And, in any case, hope for a reduction in sentence probably is one of the important motivating factors in the minds of most prisoners who volunteer as research subjects. A well-known prisoner who participated as a volunteer in a number of experiments has described the instrumental benefits that he and his fellow prisoners anticipated. Nathan Leopold, who in 1924 as a youth of 19 committed with Richard Loeb what was publicized

*Mr. D. was hospitalized on the Metabolic Research Ward described by Fox.[8]

as the "crime of the century," the murder of 14-year-old Bobby Franks, and who was sentenced to "life plus 99 years," has described one of his reasons for volunteering for an experimental malaria study as follows:

"There was no assurance whatever that volunteers would be rewarded by having their time cut. Of that fact each group was solemnly and emphatically reminded before they were allowed to sign their contracts. But the possibility did exist that there would be time cuts. And that was a chance I could not afford to miss . . . . I had some reason to hope that public opinion in my regard might be softened to some degree . . . ."[17]

The hopes of Leopold and the other 441 inmates of Stateville Penitentiary in Illinois who offered themselves as volunteers on the malaria project were eventually fulfilled. He and most of the other prisoner-volunteers achieved their goal; they were granted either commutation of sentence or parole as a direct reward for their service.[17] When pellagra experiments were carried out by Goldberger on convict volunteers in 1915, formal agreements were drawn up before the experiment with their lawyers for their subsequent pardon and release.[27]

Another important instrumental function that acting as a research subject can have is an economic one. Under certain circumstances, persons who volunteer to serve in this capacity are financially rewarded for doing so. For some ill persons and p[illegible]ners, this may be one of the few po[illegible]e ways of earning some money open to them. As for the well persons and those with good standing in the eyes of society who volunteer for this role, the money payments sometimes offered to them may be a desirable or necessary supplement either to the financial resources provided by another full-time job or some temporarily unremunerative role, such as that of student. For example, one study of the reasons why 56 healthy, young male college students, aged 21 to 28 years, volunteered to receive one or more drugs as part of a medical experiment found that "a number of them [did so] primarily for monetary rewards."[16] It is known that many medical students volunteer as research subjects because it provides them with a convenient, professionally relevant way of earning some money in the course of the long, expensive process of training they undergo. Occasionally also, reference is made to a "unique group of 'professionals' who make a . . . livelihood by selling their bodies and blood for tests."[22]

For those persons in our society who are conscientious objectors, acting as a research subject may have still another kind of instrumental function. Under the United States Selective Service Act it is possible for a selectee to fulfill his military obligation for two years' service by contributing to "the maintenance of the national health, safety, or interest" as a volunteer research subject. According to one estimate, "4000 Quakers, Mennonites, members of the Assemblies of God and Church of the Brethren, or other pacifist sects . . . choose this course each year."[35] The Clinical Center at Bethesda, for example, has established a permanent corps of normal volunteers for medical experiments by developing contractual agreements with these "peace churches." "Young people enrolled in the church public service movements are permitted to select health research as a type of citizen duty equivalent to military service for some of the candidates."*[15]

Like the money, facilities, and positions available to American pl[illegible]ians for the conduct of clinical med[illegible] experiments, the instrumental rewards connected with volunteering to act as research subject are partly the result of the rather extraordinary degree to which persons in our society believe in the practical importance and moral excellence of scientific research in general and medical research in particular. This is perhaps most clearly seen when we consider the basic premises that seem to underlie the arrangements made for prison-

*Doctor (of Law) I. Ladimer initiated this program when he was Assistant Director of Research Planning for the National Institutes of Health.

ers and conscientious objectors to participate as research subjects, and the way that such participation is regarded by the larger society. With respect to conscientious objectors, as already indicated, the American Government considers service as a medical research subject an act of good citizenship which makes an important contribution to the national welfare fully equivalent to military service. And Governor Green's Committee[9] has this to say about "acceptable prisoner volunteers": "Since one of the purposes of the parole system is reformative, the reformative value of serving as a subject in a medical experiment should be considered. Serving as a subject in a medical experiment is obviously an act of good conduct, if frequently unpleasant and occasionally hazardous, and demonstrates a type of social consciousness of high order when performed primarily as a service to society." The point of view expressed here is: Participating as a research subject is a commendatory moral-social act because it entails willingness to undergo discomfort and risk partly for the sake of contributing to the larger good of health and welfare in our society. What is more, quite apart from their original motivation for doing so, the experience of acting as a research subject has a morally elevating effect on persons who serve in this capacity. For these reasons, the possibility of granting some degree of clemency to each prisoner who volunteers for medical research ought to be considered.

The fact that acting as a volunteer subject for medical research is regarded widely and to some extent "officially" in our society as admirable, even heroic, contributes to two other sorts of functions that this role may serve for those who undertake it. Playing the role of volunteer research subject enables some people to express symbolically certain secular and sacred values that are highly approved in our society. Partly as a consequence, this role is also a way for persons to achieve private and public expressions of honor from medical scientists and the nonmedical public.

Besides wanting to have their sentences reduced, prisoners sometimes use the volunteer research subject role for value-symbolic functions. During World War II American prisoners found in the role a way of serving their country, of expressing commitment to its democratic and humanitarian values, and of paying a part of the heavy debt they felt they owed their society for having broken its laws and violated its morality. These functions are illustrated in Nathan Leopold's[17] account:

> "The coming of the malaria project was probably the most stirring and exciting event of my prison term. Here, without any question, was a real chance to be useful. . . . This was a real problem, a real challenge. The length of the war in the Pacific could be very well affected by those who got the answer to malaria first. . . . In some not too farfetched sense our bodies would be the battlefield in a not unimportant war. . . .
>
> "There were some who, I am convinced, went into the thing entirely on an idealistic basis. They didn't want the money . . . and they had little hope of getting their sentences reduced. But they saw a chance to do something decent and worthwhile for a change. They were more than willing to undergo the necessary discomfort and run the necessary risk in order to make their tiny contribution to humanity. . . ."

Closely related humanitarian values are often expressed by patients, medical ancillaries such as students, nurses, and technicians, and by medical investigators themselves, in volunteering as research subjects. As one such patient volunteer subject put it, "Medical science snatched me from the clutches of a sure death. . . . I hope that my submission to these experiments will do the same for other men and women in the years to come."* The humanitarian value of their volunteering is often primary for those patients who have been told that their own chances for deriving help from the experiments conducted on them are quite small.

*Case of William J. Barber in Fox.[8] Mr. Barber was one of the early patients to volunteer for experiments with the then-new drug ACTH.

"It is the experience of many physicians," says Shimkin,[31] "that this type of patient often wants, and often demands that something be done for advancement of knowledge if not for personal benefit."

Through volunteering to act as research subjects themselves (as well as through conducting experiments on others), medical investigators often express their value-commitment to the advancement of scientific knowledge and the reduction of some of the suffering that illness inflicts on humanity. Such sentiments were movingly put into words by Walter Reed in a letter he wrote to his wife from Cuba on New Year's Eve, 1900, concerning the yellow fever experiments that he and other volunteer subjects had undergone: "The prayer that has been mine for twenty years, that I might be permitted in some way or at some time to do something to alleviate human suffering, has been granted. A thousand Happy New Years."[3]

Throughout medical history, many investigators have acted as subjects for their own research. Their reasons for doing so have been instrumental as well as value-symbolic. For particularly when the experimental procedures or agents medical investigators wish to try involve uncertainties, discomforts, or potential risks of such magnitude that they do not think it justifiable to ask other persons to act as subjects, or they encounter difficulty in finding individuals willing to expose themselves to this degree of ambiguity and danger, one of the only moral and practical ways in which they can carry out such an experiment is to act as their own research subjects.

Religious values of certain kinds have also been expressed in the volunteer research subject role. As we have indicated, two American "peace churches" in particular, the Church of the Brethren and the Mennonites, urge their younger adherents to volunteer. Many have undertaken this role not simply because it has given them a practical way to meet their military service requirements, but also because it has enabled them to express what they feel is a higher spiritual value than serving in the armed forces, and to make what they consider to be religiously relevant progress in their own personal development. For example, in a newspaper article, James Tomlison, "an athletic 21-year-old from Goshen, Indiana," is quoted as saying, "I have been in the Church of the Brethren all my life. My reason [for volunteering as a research subject] stems from my training in the church. . . . I wanted the experience to help develop my character, since I would like to become a minister."[33]

It is primarily because of some of its value-symbolic functions that the role of volunteer research subject and those who play it are so highly regarded by medical investigators and the lay public. For in a number of ways this role seems to epitomize some of the cardinal values of American society. Ours is a society with a high regard for active, rationally based mastery of life and for any sort of achievement that blends individualism and a humanitarian sense of social responsibility. We are inclined to glorify our frontier, pioneering tradition and spirit. We have a special appreciation for the pragmatic and ethical value of science in general, and also for its particular contribution to the realization of another one of our important values, good health.[21,28] In the role of volunteer research subject, these values are brought together and played out in a way that is regarded with a great deal of social approval. For, of their own volition, partly with humanitarian goals in view, research subjects endure the discomforts, uncertainties, and hazards of pioneering experiments and thus make a contribution to our rational mastery of the problems of health and social welfare.[28]

A question that our analysis of the value-symbolic and prestige functions of the role of volunteer research subject raises is: How specific to American society are these functions? Does this role have these same, equally cogent functions in this regard in other modern Western societies? An editorial by *New York Times* journalist, James

Reston,[29] which pays tribute to the seven men who have been chosen from a larger group of volunteers to be trained as candidates to pilot the first manned rocket flight into space, suggests that volunteering to participate in scientific experiments "fits" ultimate American values in a rather special way:

"Those gloomy students of the American character who think we've lost the hop on our fast ball should have been around here this week when seven young American men dropped into Washington on their way to outer space. . . . What made these . . . intelligent, plain-speaking, small-town fliers . . . so exciting was not that they said anything new but that they said all the old things with such fierce convictions. They talked of the heavens the way the old explorers talked of the unknown seas. They wanted to see what was 'on the other side.' They spoke of 'duty' and 'faith' and 'country' like Walt Whitman's pioneers. . . . All confessed to a religious conviction that they would come back. . . . Nobody went away from these young men scoffing at their courage and idealism. . . . Officials . . . were almost startled to hear, not only the ancient American cry that 'the sky's the limit,' but that it's just the beginning. . . ."

The public attitudes admiring of volunteer research subjects are expressed in an article in a national general circulation magazine[5]:

"How would you like to make a voluntary parachute jump from a height of seven and a half miles, or deliberately inhale the deadly new nerve gases that snuff human lives in the same dreadful way that DDT kills insects, or allow yourself to be paralyzed completely by an injection of curare, the substance used by South American Indians on their poisoned arrows?

". . . there are almost 500 persons in this country who have taken these risks or worse, for the noblest of reasons. And they do it so regularly that they have banded together . . . . Their organization is the Walter Reed Society, named for the famous band of volunteers who contracted yellow fever to help Major Reed solve the mystery of that once-deadly disease . . . .

"The members . . . are, for the most part, young medical students and scientists whose only aim is to help humanity. . . .

". . . There is also a sprinkling of patients who have volunteered to be studied for the possible benefit of others, even though they can expect no improvement in their own condition . . . .

"[One of the] functions of the Walter Reed Society is that of granting recognition to human guinea pigs. Membership is by invitation, and each member receives a certificate commending him for the self-sacrifice through which he has 'made a gift toward greater knowledge for the maintenance of health, the relief of suffering, and the prolongation of life to all peoples of the earth.' "

The article also reveals how special segments of the public band together to bestow prestige on volunteers whom they know to be deserving and whom they hope to celebrate for the larger, less well-informed public all around them. The Walter Reed Society is not unique, though it is perhaps the association most specifically devoted to honoring volunteers. In addition there are such associations, with other functions as well—for example, the Adrenalectomy Club[8] (formed by patients who underwent a radical experimental operation involving the removal of their adrenal glands), the Mended Hearts Club (founded by patients who had experimental cardiac surgery), and the Malaria Volunteers[17] (comprised of prisoners who participated in malaria experiments).

As we have already seen, prestige is privately and publicly bestowed on persons who serve as research subjects not only by special associations, but also by the medical investigators for whom they participate in experiments.

Finally, as the formation of associations like the Adrenalectomy Club, the Mended Hearts Club, and the Malaria Volunteers indicates, when a number of persons acting as research subjects in our society are housed or hospitalized in the same place, in the words of one patient-subject they often "get close-knit together." They tend to develop an informal community, which in some cases may evolve into a formal as-

sociation or club. The unity and identification with one another that research subjects develop in these circumstances seem to help and motivate them to meet some of the discomforts and risks associated with the role they have undertaken. From their association with one another, research subjects often derive a sense of belonging to an intimate, exclusive, admirable, and likeable group of persons who are "contributing to medical science," "benefiting humanity," "having good times together," and helping one another with the problems they share. Thus, the experiences, values, and camaraderie they share provide research subjects with psychological support and gratification that offset some of the strains they experience or, at least, partly compensate them for these strains.

Such a community of research subjects is not only organized around a shared commitment to each other and to the advancement of medical science, but also to the medical investigators conducting the experiments, who, as we saw earlier, often regard and treat research subjects as colleagues and friends. The intimate, semipersonal, semiprofessional relations that become established between medical investigators and their subjects, as well as the "red carpet treatment" in the living and food arrangements that the persons who act as subjects are given, provide psychological gratifications which make the strains of experimentation more acceptable to them:

> ". . . When you're on a constant diet, for instance," says a patient-subject, "You could drink a little more than [the doctors] want you to; eat in between meals—things like that. But when they explain things to you and they're so nice to you as they are here, you don't have the desire to cheat. You don't even feel resistance inside. . . ."[8]

Many patient-volunteers in this situation seem to enjoy what the psychiatrist would term "secondary gains" from this role; some establish "transference" relations with medical investigators from which they derive important emotional satisfactions. Or, as Leopold indicated, the comfort, privileges, and trust that he and his fellow-prisoners were granted as volunteers made them feel that they were "on the same side of the fence . . . partners in a common endeavor" with the Army doctors for the benefit of society, which, in turn, gave them "more solid, lasting satisfaction from what they were doing than many of them had known in some time."[17]

Although the formation of a special kind of association or community by persons who act as research subjects may not be uniquely American, the values and institutions of our society seem to exert some influence in this regard. An example of a club formed by European patients who had undergone a radical experimental procedure (a pneumothorax) occurs in Thomas Mann's *The Magic Mountain.* In the Swiss tuberculosis sanatorium which is the site of Mann's novel, patients organize a Half-Lung Club.

Since the days of De Toqueville,[6] it has often been noted that one of the characteristic features of our society is the extraordinary number of private groups and associations that have been organized around special interests. On the basis of these general empirical grounds and of more specific observations of medical research units that we ourselves have made both here and abroad, we venture the guess that there is more of a tendency in the United States than in European societies for research subjects to form such groups and to find social-psychological satisfactions in them that help to compensate for some of the stress they undergo in this role.

We hope to explore further these still-tentative ideas about social and cultural factors that facilitate or impede clinical medical research on human subjects, here and abroad, as we continue the study we have begun in Europe.

Appendix

Although we have not discussed this in the body of this paper, we would like to

indicate our recognition of the role that more individualistic, personality-determined psychological factors undoubtedly play in motivating persons to volunteer as research subjects. Some recent studies suggest that persons with certain kinds of personalities are more inclined to find special psychological gratifications in this role. For example, when Rohrschach tests and psychological interviews were given to the 56 healthy, male college students serving as volunteer subjects in pharmacologic experiments, it was found that the incidence of serious psychological difficulties was approximately twice as high as would be expected in an unselected college population.[16] Or again, a series of intensive psychiatric interviews conducted by Dr. Sanford Gifford* with two normal college students who volunteered to take large doses of ACTH and cortisone showed them counterphobic personality structures with the active emotional need to "maintain the invulnerability of [their] bodies . . . against any threatened internal and external change . . . through the supremacy of physical activity," and the passive need to "submit . . . to a series of repetitious ordeals that test and probe this invulnerability." The role of experimental subject, Dr. Gifford concludes, "furnishes an ingenious and socially acceptable way for gratifying both . . . needs simultaneously, a means of enacting the role of 'Chasseur Alpine' while reclining in bed."

The evidence from these two studies is perhaps enough to emphasize the importance of further investigating how various psychological motives combine with different social functions to attract individuals to this role and enable them to find gratifications in it. It would also be interesting and pertinent to learn more about the kinds of personality traits that incline physicians to engage in clinical research or, at least, make it more probable that they will be able to tolerate the strains of this role and find real satisfaction in it. Finally, it would be theoretically and practically edifying and valuable if some attempt were made to ascertain whether the personality traits which attract and fit persons to the roles of research subject and clinical investigator, respectively, occur more frequently in some societies than others.

*Gifford, S.: A Note on the Motivation of the Experimental Subject: Interviews With Two Normal Subjects During the Administration of Steroid Hormones, unpublished paper.

I wish to thank Professor Bernard Barber (Department of Sociology, Barnard College, Columbia University) for his advice and help in the writing of this article.

References

1. Beecher, H. K.: Experimentation in Man, Springfield, Ill., 1959, Charles C Thomas, Publisher, pp. 1-80.
2. Bowers, J. Z.: The Study of Medical Education in the United States, J. M. Educ. **34**:1134-1138, 1959.
3. Cannon, W. B.: The Career of the Investigator, in Samuel Rapport and Helen Wright, editors: Great Adventures in Medicine, New York, 1952, The Dial Press, pp. 508-516.
4. Crabbé, J.: Le climat de la recherche médicale aux États-Unis, Praxis (Rev. suisse de méd.), No. 24, June 11, 1959, pp. 561-562.
5. Davidson, B.: So He Took the Cobra Venom and Shot It Into His Arm, Collier's Nov. 1, 1952, pp. 52-55.
6. De Toqueville, A.: Democracy in America II. New York, 1954, Vintage Books, Alfred A. Knopf, Inc., pp. 117-118.
7. Du Bois, E. F.: The First Metabolism Ward of the Russell Sage Institute of Pathology, in Methods and Problems of Medical Education, 1928 (no volume or page numbers available).
8. Fox, R. C.: Experiment Perilous, Glencoe, Ill., 1959, The Free Press, pp. 1-262.
9. Green Committee: Ethics Governing the Service of Prisoners as Subjects in Medical Experiments, J.A.M.A. **136**:457-458, 1948.
10. Guttentag, O. E.: Problems of Experimentation on Human Beings: II. The Physician's Point of View, Science **117**:207-210, 1953.
11. Jefferson, G.: Man as Experimental Animal, Conquest **43**:2-11, 1955.
12. Kourilsky, R.: Leçon inaugurale (on assuming Chaire de Clinique Médicale, Faculté de Médecine de Paris), 20 novembre 1958, Paris, L'Expansion Scientifique Française, pp. 1-32.
13. Kreighbaum, H.: Science, The News, and The Public, New York, 1958, New York University Press.
14. Ladimer, I.: Human Experimentation: Medi-

colegal Aspects, New England J. Med. **257**:18-24, 1957.
15. Ladimer, I.: May Physicians Experiment? Internat. Rec. Med. **172**:586-598, 1959.
16. Lasagna, L., and von Felsinger, J. M.: The Volunteer Subject in Research, Science **120**:359-361, 1954.
17. Leopold, N. F.: Life Plus 99 Years, New York, 1958, Doubleday & Company, Inc., pp. 1-381.
18. Lewis, T.: Research in Medicine and Other Addresses, ed. 2, London, H. K. Lewis & Co., Ltd. (no date given), pp. 1-102.
19. Lister, J.: By the London Post, New England J. Med. **261**:1125-1126, 1959.
20. Means, J. H.: Ward 4: The Mallinckrodt Research Ward of the Massachusetts General Hospital, Cambridge, Mass., 1958, Harvard University Press, pp. vii-187.
21. Merton, R. K.: Science and Democratic Social Structure, in Social Theory and Social Structure, Glencoe, Ill., 1949, The Free Press, pp. 307-316.
22. New York Times, Oct. 6, 1952.
23. New York Times, Jan. 4, 1960.
24. New York Times, Jan. 24, 1960.
25. Nuremberg Military Tribunals, Trials of War Criminals (The Medical Case), Volume 2, Washington, 1947, U.S. Government Printing Office, pp. 181-184.
26. Pasteur Vallery-Radot, L.: Le Secret médicale doit être respecté, Chapter II in Médecine à l'échelle humaine, Paris, 1959, Librairie Artheme Fayard, pp. 29-46.
27. Parsons, R. P.: Joseph Goldberger and Pellagra, in Samuel Rapport and Helen Wright, editors: Great Adventures in Medicine, New York, 1952, The Dial Press, pp. 586-605.
28. Parsons, T.: The Definition of Health and Illness in the Light of American Values and Social Structure, in E. Gartly Jaco, editor: Patients, Physicians and Illness, Glencoe, Ill., 1958, The Free Press, pp. 165-187.
29. Reston, J.: The Sky's No Longer the Limit, New York Times, April 12, 1959.
30. Science, June 12, 1959, p. 1597.
31. Shimkin, M. B.: The Problem of Experimentation on Human Beings: I. The Research Worker's Point of View, Science **117**:205-207, 1953.
32. Shorr, E.: Emergence of Psychological Problems in Patients Requiring Prolonged Hospitalization, in Molly Harrower, editor: Medical and Psychological Teamwork in the Care of the Chronically Ill, Springfield, Ill., 1955, Charles C Thomas, Publisher, pp. 32-38.
33. Shuster, A.: Why Human Guinea Pigs Volunteer, New York Times, April 13, 1958, pp. 62-63 and 67.
34. S.S.: Special news article in La Libre Belgique, Dec. 3, 1959.
35. Time, Sept. 27, 1954.

(To be continued)

The diuretic action of trichlormethiazide in patients with congestive heart failure

A double blind study was carried out to determine the dose-response relationships of trichlormethiazide, 3-dichloro-methyl-6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, when given by repeated oral administration to patients with chronic congestive heart failure.

Significant diuretic responses were observed following oral doses of 2, 4, and 8 mg. trichlormethiazide twice daily for one week. Similar diuretic responses occurred after 8 mg. trichlormethiazide and 75 mg. hydrochlorothiazide, the relative activity of trichlormethiazide and hydrochlorothiazide being in the order of 10:1. No significant changes in serum creatinine concentrations were observed in these patients treated with trichlormethiazide in doses as high as 8 mg. twice daily for one week. Trichlormethiazide did not alter serum sodium, potassium, chloride, or carbon dioxide combining power significantly. A decrease in serum osmolality was noted, however, after the diuretic responses to both trichlormethiazide and hydrochlorothiazide.

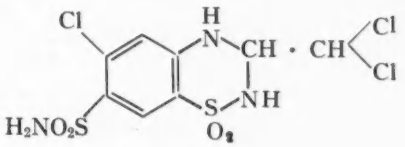
Duncan E. Hutcheon, M.D., and Teruo Takasu, M.D. *Jersey City, N. J.*
Departments of Pharmacology and Medicine, Seton Hall College of Medicine and Dentistry, and the Jersey City Medical Center

Trichlormethiazide* is a 3, 6-substituted benzothiadiazine which has recently been found to be an active diuretic agent. In both experimental animals and man, trichlormethiazide was shown to have more than five times the diuretic potency of hydrochlorothiazide.[1,8] Electrolyte excretion patterns revealed that trichlormethiazide increased sodium and chloride excretion without changing urinary pH.

Once the diuretic response to single doses of trichlormethiazide had been established, interest centered on a study of its effects on repeated administration in chronic edematous states. Previous experiments have shown that the activity of diuretic agents can be compared quantitatively in patients with edema when the drugs are given over periods of one week at each dosage level.[4,7] The following study, therefore, was carried out to determine the dose-response relationships of trichlormethiazide when administred on a chronic basis to patients with congestive heart failure. Trichlormethiazide in doses ranging between 1 and 8 mg. and hydrochlorothiazide in a dose of 75 mg. were administered orally. Each dose was given twice daily over a period of 7 days. Weight loss during the period of therapy was used as a measure of

*Supplied as Naqua by the Schering Corporation.

diuretic response. Changes in serum electrolytes, creatinine, and osmolality during these periods of diuretic therapy were also recorded.



Trichlormethiazide

Methods

The studies were carried out in 9 ambulatory patients with congestive heart failure attending the Cardiac Clinic of the Jersey City Medical Center at weekly intervals. Two patients had rheumatic heart disease while the others had arteriosclerotic heart disease. All patients were on maintenance digitalis therapy (0.1 mg. digitoxin or 0.1 Gm. digitalis leaf daily) during the course of the experiment. Diuretic therapy was given every other week, alternating with one-week periods of placebo therapy to each of the 9 patients as shown in Fig. 1. Trichlormethiazide was given in doses of 1, 2, 4, and 8 mg. Hydrochlorothiazide was administered in a dose of 75 mg. for comparison. Drugs and placebo were made up in capsules of the same appearance and the drugs were supplied under code to satisfy the requirements of a double blind study. The doses of trichlormethiazide and hydrochlorothiazide were assigned to the patients according to a randomized block design. The following measurements were made weekly at the end of the periods of diuretic and placebo therapy: body weight, serum sodium, potassium, chloride, carbon dioxide combining power, creatinine, and osmolality. Diuretic response was indicated by the decrease in body weight over the period of drug therapy.

Results

Diuretic responses. The sequence of changes in weight and serum electrolytes in 1 of 9 patients with congestive heart failure, who received placebo and diuretic therapy with trichlormethiazide and hydrochlorothiazide on alternate weeks, is shown in Fig. 1. In Table I the changes in body weight produced by the oral administration of trichlormethiazide and hydrochlorothiazide in all 9 patients are compared. Significant weight losses were noted during one week of therapy with 2.0, 4.0, and 8.0 mg. trichlormethiazide and 75 mg. hydrochlorothiazide twice daily. One milligram trichlormethiazide twice daily by the oral route was below the threshold diuretic dose for 3 of the 9 patients in this series. Similar diuretic responses were produced by 8 mg. trichlormethiazide and 75 mg. hydrochlorothiazide. The decreases in body weight occurring during the periods of diuretic therapy were believed to be due to a loss of edema fluid since there were no changes in the patients' appetites, diets, or physical activities to account for them.

Effects on serum electrolytes. Serum sodium and chloride levels were not altered by trichlormethiazide in doses as high as 8 mg. twice daily for one week (Table II). Hydrochlorothiazide at a dose of 75 mg.

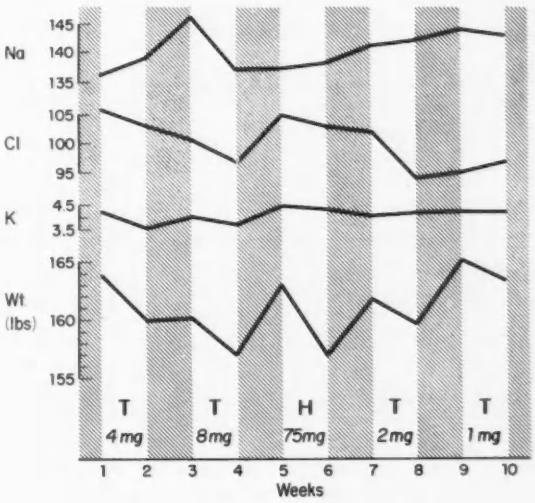


Fig. 1. Changes in serum electrolytes (milliequivalents per liter) and body weight (pounds) in 64-year-old white woman with rheumatic heart disease, mitral stenosis, and congestive heart failure. *T*, trichlormethiazide; *H*, hydrochlorothiazide. The shaded columns indicate periods of placebo therapy.

Table I. *Changes in body weight (pounds) during one week of diuretic therapy. Doses given twice daily for 7 days*

Case	*Trichlormethiazide*				*Hydrochlorothiazide*
	1.0 mg.	*2.0 mg.*	*4.0 mg.*	*8.0 mg.*	*75 mg.*
1	−1.8	−0.5	−0.8	−0.5	−2.2
2	−1.0	−10.0	−1.0	−1.8	−6.2
3	−1.8	−2.0	−3.8	−3.2	−6.0
4	+1.2	−5.0	−1.5	−7.2	−1.5
5	+3.0	−4.5	−3.5	−0.2	−5.5
6	−3.5	−2.7	−6.8	−9.0	−7.0
7	−4.5	—	−7.5	−9.2	—
8	+0.2	−2.5	−0.8	−3.2	−3.2
9	−1.2	−0.2	+0.5	−2.0	−1.2
Mean	−1.05	−3.42*	−2.80*	−4.03†	−4.10†
s.e.	±0.76	±1.11	±0.94	±1.17	±0.82

*p < 0.05.
†p < 0.01.

Table II. *Serum electrolytes (milliequivalents per liter) after one week of diuretic therapy (mean± s.e.). Doses given orally twice daily*

	Dose (mg.)	*Na*	*K*	*Cl*	*CO_2*
Trichlormethiazide	1.0	141 ± 1.2	4.3 ± 0.1	99 ± 1.9	21.0 ± 0.8
	2.0	140 ± 1.2	3.9 ± 0.2	98 ± 2.0	20.2 ± 1.7
	4.0	140 ± 1.1	4.0 ± 0.2	100 ± 1.2	20.9 ± 1.4
	8.0	139 ± 0.7	3.7 ± 0.2	96 ± 2.0	20.1 ± 1.4
Hydrochlorothiazide	75	138 ± 1.6	3.7 ± 0.1	98 ± 2.0	21.1 ± 1.1
Control		140 ± 0.1	4.1 ± 0.1	100 ± 0.9	20.9 ± 0.8

Table III. *Serum creatinine concentrations and osmolality after one week of diuretic therapy*

	Dose (mg. twice daily)	*Creatinine (mg./100 ml.)*	*Osmolality (mOs./Kg. H_2O)*
Control		1.63 ± 0.07	292 ± 1.2
Trichlormethiazide	1.0	1.68 ± 0.18	287 ± 3.3
	2.0	1.73 ± 0.19	289 ± 1.5
	4.0	1.68 ± 0.17	286 ± 1.9*
	8.0	1.71 ± 0.19	285 ± 2.7*
Hydrochlorothiazide	75.0	1.62 ± 0.13	287 ± 1.1*

*p < 0.05.

twice a day for 7 days failed to alter serum sodium and chloride concentrations. A 10 per cent decrease in serum potassium was noted after one week of diuretic therapy with 8 mg. trichlormethiazide and 75 mg. hydrochlorothiazide twice daily. These changes in serum potassium, however, were not statistically significant.

There were no significant changes in serum carbon dioxide combining power in

these 9 patients during the weekly periods of diuretic therapy with trichlormethiazide and hydrochlorothiazide.

Effect on serum creatinine levels. In Table III the serum creatinine concentrations in each of the 9 cases of congestive heart failure are compared before and after the period of diuretic therapy. Serum creatinine concentrations remained within normal limits during the one week of therapy with either trichlormethiazide or hydrochlorothiazide.

Serum osmolality and pH. Serum osmolality was determined cryoscopically with the Fiske osmometer at the end of the weekly periods of placebo and diuretic therapy. A slight but statistically significant lowering of serum osmolality occurred in patients treated with diuretic doses of trichlormethiazide and hydrochlorothiazide. No significant changes in serum pH were observed after trichlormethiazide in doses of 1 to 8 mg. twice daily for one week.

Discussion

Previous studies have shown that diuretics can be compared quantitatively in patients with congestive heart failure with weight loss used as a measure of diuretic response. Gold and his colleagues,[2,3] for example, assayed the diuretic activity of the organic mercurials and carbonic anhydrase inhibitors by determining the effects of these drugs on body weight. Recently Kwit, Gold, Hughes, Golfinos, and Goessel[6] reported that 24 hour weight loss after a dose of diuretic is the most stable index of the edema-clearing effect. Hutcheon, Schwartz, and Condouris[4] found that weight loss could also be used to estimate diuretic potency in ambulatory patients with congestive heart failure when the drugs were given over a period of one week at each dose level. The data in both the acute and chronic human studies could be analyzed according to the same statistical methods established for other biologic assay procedures.

In the present study the diuretic actions of trichlormethiazide and hydrochlorothiazide have been compared under conditions which approximate those of chronic diuretic therapy in man. Similar diuretic responses were observed following 8 mg. trichlormethiazide and 75 mg. hydrochlorothiazide when these doses were given twice daily for 7 days. These results agree with the data obtained from acute experiments which indicated that trichlormethiazide was approximately 10 times as potent as hydrochlorothiazide on a milligram-for-milligram basis.[8]

In spite of the fact that all patients were on digitalis maintenance therapy, no abnormalities in serum electrolytes were observed after trichlormethiazide was given in diuretic doses over a period of one week. Trichlormethiazide also failed to increase serum creatinine concentrations in these patients. The results of laboratory experiments showed that trichlormethiazide did not interfere with creatinine clearance and glomerular filtration rate.[8]

A decrease in serum osmolality was noted after diuretic doses of trichlormethiazide and hydrochlorothiazide. The natriuresis produced by chlorothiazide and hydrochlorothiazide has been attributed to an interference with sodium reabsorption at both the proximal and distal tubule.[5] By depressing sodium reabsorption in the diluting segment of the distal tubule, these drugs were found to reduce the production of solute-free water. The dilution of the serum during diuresis by the benzothiadiazine compounds could therefore be explained by an action of these drugs in preventing sodium reabsorption in the distal diluting segment of the nephron.

The authors wish to express their appreciation to Dr. M. L. Schwartz, Director of the Cardiac Clinic, Jersey City Medical Center, and the Essex County Heart Association, for their support.

References

1. Ford, R. V.: The Clinical Pharmacological Investigation of a New Benzothiadiazine Diuretic, CMR-807, Am. J. Cardiol. 5:407-412, 1960.
2. Gold, H., Greiner, T. H., Warshaw, L., Kwit, N. T., and Ganz, A.: Diuretic Action of Two

Carbonic Anhydrase Inhibitors in Congestive Failure, J.A.M.A. **167**:814-818, 1958.

3. Greiner, T. H., Gold, H., Bliss, C. I., Gluck, J., Marsh, R., Mathes, S. B., Modell, W., Otto, H., Kwit N. T., and Warshaw, L.: Bioassay of Diuretic Agents in Patients With Congestive Failure, J. Pharmacol. & Exper. Therap. **103**:431-440, 1951.
4. Hutcheon, D. E., Schwartz, M., and Condouris, G. A.: Comparison of Orally Active Diuretics in Congestive Heart Failure, Fed. Proc. **18**:405, 1959.
5. Januszewicz, W., Heinemann, H. O., Demartini, F. E., and Laragh, J. H.: A Clinical Study of the Effects of Hydrochlorothiazide on the Renal Excretion of Electrolytes and Free Water, New England J. Med. **261**:264-269, 1959.
6. Kwit, N. T., Gold, H., Hughes, J. H., Golfinos, A., and Goessel, E. A.: Relative Diuretic Efficacy of Diuril and Mercuhydrin in Congestive Failure, Pharmacologist **1**:52, 1959.
7. Schwartz, M. L., Hutcheon, D. E., Aygen, M., and Condouris, G. A.: Diuretics in Congestive Heart Failure, J. M. Soc. New Jersey **57**:69-73, 1960.
8. Taylor, R. M., Mershon, J. S., and Winbury, M. M.: Pharmacology of a New Benzothiadiazine Diuretic, Fed. Proc. **19**:364, 1960.

The accumulated literature in every department of science is already so enormous and is increasing at such a rapid rate that any association or individual undertaking to contribute thereto should do so only under a sense of grave moral responsibility.

FROM DR. HENRY P. BOWDITCH, PROC. AM. ASSOC. ADV. OF SCIENCE **35**:237, 1887.

Estrogen therapy in men with myocardial infarction: Occurrence of lipid changes before feminization

Beneficial results of estrogen administration on blood lipids can be obtained without production of breast tenderness or other evidence of feminization according to a study of 16 male outpatients with myocardial infarction who received small and moderate doses of estrogen daily. Inasmuch as serum cholesterol levels and cholesterol/phospholipid ratios were lowered before development of breast tenderness and no further change resulted despite average doubling of estrogen dosage and increased time on therapy, it is apparent that the administration of estrogen short of the amount producing breast tenderness is fully as effective as much larger doses in providing the cholesterol-lowering effects of estrogen.

Jessie Marmorston, M.D., Frederick J. Moore, M.D., J. J. Lewis, M.D., Oscar Magidson, M.D., and Oliver Kuzma, M.D. *Los Angeles, Calif.*
Departments of Medicine and Public Health, University of Southern California School of Medicine, the Los Angeles County Hospital, and the Cedars of Lebanon Hospital

The ability of estrogens to alter serum lipids in men and women in the direction or normal[1-3,8,10-13] suggests that estrogen may be useful in the prevention of myocardial infarction. One important drawback to the use of estrogen is the tendency of exogenous estrogen to cause feminization in men, with hypertrophy of glandular tissue of the breast, loss of drive, libido, and potency, and atrophy of the testes. According to a study now in progress, serum lipid changes occurring under therapy with small and moderate dosages of estrogen and without feminizing side effects may be fully as great as serum lipid changes produced in these same patients with larger dosages of estrogen which elicit side effects.

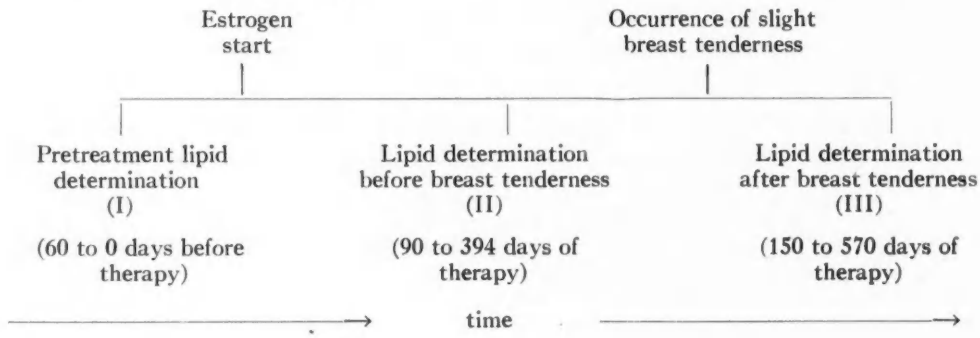
Aided by grants from the Albert and Mary Lasker Foundation and by grants H-2198, H-2199, and H-2701 from the National Heart Institute. We are indebted to Dr. Kenneth Ericson of Organon, Inc., for supplies of Lynoral (ethinyl estradiol), to Dr. Irwin C. Winter of G. D. Searle & Co. for Manvene (SC 6924, 3 methoxy-16, -methyl-1,3,5 (10)-estriene-16,B,17,B-diol), and to Dr. John J. Jewell of the Ayerst Laboratories for Premarin (mixed conjugated equine estrogen, NND) used in these studies.

Clinicians participating in these studies were Drs. Ralph Alexander, Jacob Bernstein, Irving Gordon, William Grant, Jack J. Lewis, Fletcher McBroom, Joseph Walker, and Albert White. Laboratory determinations were made under the direction of Drs. John W. Mehl, Ross Jacobs, and Sara M. Myers.

Method

Sixteen of our men patients with unequivocal evidence of coronary artery disease, who had received estrogen therapy for at least 3 months without developing any feminizing side effects, and who later demonstrated mild breast tenderness as a result of continued therapy or increased dosage, were studied to determine whether lipid changes are already maximal before the oc-

currence of breast tenderness or become even greater with increased time and dosage. All patients were ambulatory, cooperative, and able to attend the clinic regularly. Serum cholesterol and phospholipids were determined for each of the 16 patients prior to the start of therapy, after a minimum of 3 months of uninterrupted therapy but *before* the development of slight breast changes, and at some time *after* the development of breast tenderness. The accompanying diagram may be helpful.



The pretreatment lipid determination was made an average of 10 days before the start of therapy; the second lipid determination was made after about 4 months of continuous daily therapy; and the third lipid determination after about 8 months of therapy. An average of 40 days elapsed between the second lipid determination and the occurrence of the first breast changes (9 to 116 days).

Serum cholesterol was determined in all patients by the method of Pearson and associates[9] with alcohol-acetone extracts of the serum. Lipid phosphorus was estimated by the procedure of Lowry and co-workers.[5] Logarithmic transformation of the data was necessary to reduce skewness and improve normalcy.

Lipid changes in response to increased time and estrogen dosage

Twelve of the 16 patients were treated with ethinyl estradiol. The median time for the occurrence of breast tenderness among these patients was the 187th day, with a median daily dosage of 0.1 mg. ethinyl estradiol. Three patients were treated with methoxy-methyl-estriene-diol (MMED). The first note of breast tenderness in this group occurred at an average of 144 days, with a median dosage of 30 mg. MMED daily. Only one patient of the 16 was treated with mixed conjugated equine estrogens ("equine estrogens"). Breast tenderness occurred in this patient on the 145th continuous day of therapy, with a daily dose of 1.25 mg. "equine estrogens."

The third lipid determination (Fig. 1) was done after breast tenderness had been noted by the patients. At this time the median estrogen dosage was roughly twice the dosage received by these patients before breast tenderness was noted. At the time of the third lipid determination, dosage had been increased in 11 patients, was unchanged in 3, and reduced in 2. Information as to the types of estrogen used and the dosages employed in the two periods is given in Table I.

Average serum cholesterol levels, phospholipid levels, and cholesterol/phospholipid ratio prior to therapy, during estrogen therapy but prior to the development of breast tenderness, and after breast tenderness has been noted are given in Table II. Clearly, determinations before and after note of breast tenderness are essentially the same, and both differ considerably from pretreatment levels.

Reduction in cholesterol and increase in average phospholipid values in the first months of estrogen therapy are depicted in Fig. 1. Maximum drop in cholesterol and

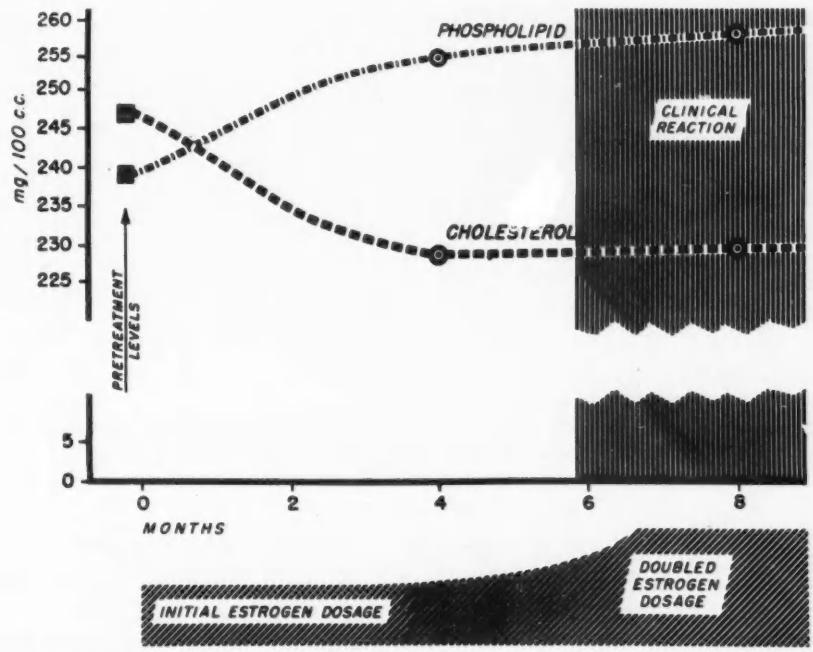


Fig. 1. Lipid changes under estrogen therapy in 16 males. Average of cholesterol levels in these patients was within normal limits prior to therapy. An attempt was made to depress these levels further by doubling the estrogen dosage. Serum cholesterol and phospholipid changes occurred before the clinical reactions. Increasing the estrogen dosage caused no further changes in the serum lipids.

rise in phospholipids occur before the development of breast tenderness, and lipid levels do not change significantly thereafter despite double estrogen dosage in the later period (see also Table II). In the 16 patients in this study, the average of the cholesterol levels was within normal limits prior to the start of therapy. An attempt was made to depress these levels further by doubling the estrogen dosage.

In previous reports[6,7] we have shown the regressions of treatment level on the pretreatment level. Using similar methods here, we have calculated the regression of each treatment value (before and after manifestations of breast tenderness) on the pretreatment value. Fig. 2 demonstrates that lipid changes occurring *before* and *after* the appearance of breast tenderness are essentially the same.

Table I. *Estrogen dosages (in milligrams) before and after breast tenderness*

Estrogen preparation	*Lipid determinations*	
	Before breast tenderness	*After breast tenderness*
Ethinyl estradiol (12 patients)	.065	.125
Methoxy-methyl-estriene-diol (3 patients)	15.0	30.0
Mixed conjugated equine estrogens (1 patient)	.625	1.875

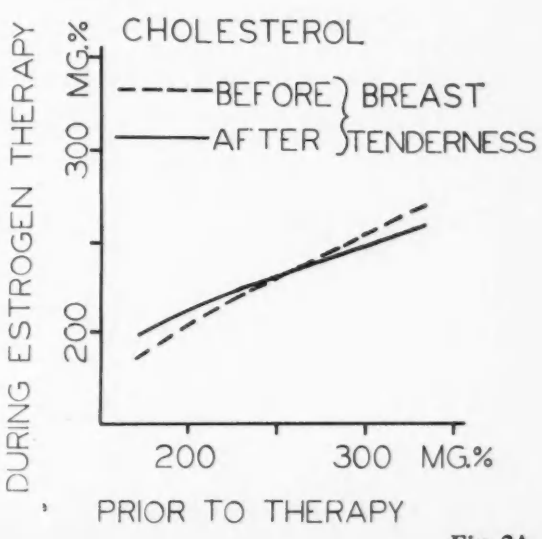


Fig. 2A.

Table II. *Effect of estrogen treatment on serum cholesterol, phospholipids, and the C/P ratio*

	Cholesterol (mg. per 100 ml.)		*Phospholipids (mg. per 100 ml.)*		*C/P Ratio*	
	Geometric mean	*90% confidence limits*	*Geometric mean*	*90% confidence limits*	*Geometric mean*	*90% confidence limits*
(I) Pretreatment	248	(230–267)	240	(221–260)	1.03	(.97–1.09)
During treatment:						
(II) Before breast tenderness	229	(208–251)	255	(229–273)	.90	(.81–1.00)
(III) After breast tenderness	230	(218–244)	259	(240–279)	.89	(.83– .96)

Discussion

Are the lipid changes observed with small or moderate doses of estrogen truly maximal, or would those lipid changes become more pronounced with time and/or increase in dosage? In an earlier paper, we[6] have reported that in women with myocardial infarction given 0.01 mg. of ethinyl estradiol for long periods of time, serum lipid changes gradually increased to a maximum and remained within normal limits. Furman and his co-workers[4] observed significant alterations in the serum lipoprotein spectrum of each of 60 male patients (none of whom manifested coronary atherosclerosis or hypercholesterolemia) *prior to the development of feminizing effects.* Their report does not indicate whether or not such changes were in fact maximal.

A study of serum lipid changes with estrogen therapy in 109 men who had suffered myocardial infarction shows that changes in lipid levels occur and become maximal *prior to* evidences of breast tenderness. Although pushing estrogen dosage beyond the tolerance of the individual patient usually will result in breast tenderness and possibly other signs and symptoms of feminization, serum lipid levels remain on the average at prefeminization levels. Apparently, increase in estrogen dosage to an average of four times the prefeminization

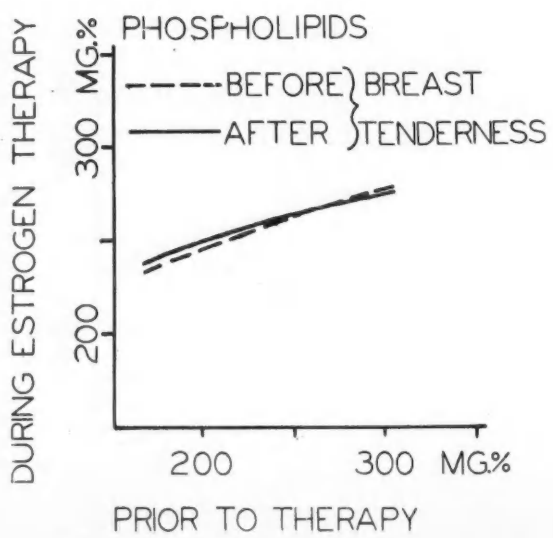


Fig. 2B.

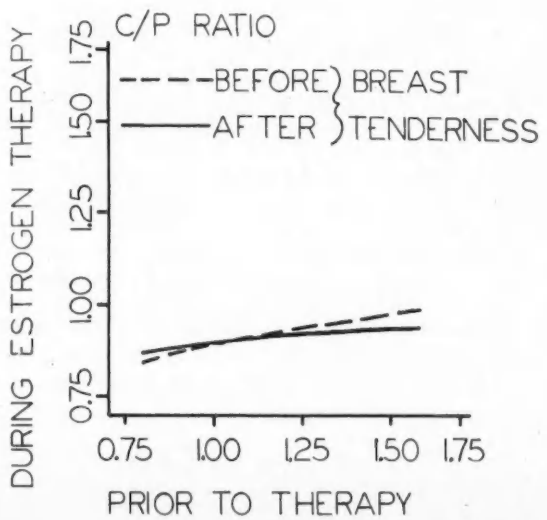


Fig. 2C.

dosage has little or no further effect on serum lipid levels.

The serum lipid changes noted in this study are fully as great as the lipid changes induced by other investigators with the administration of considerably larger doses of estrogen. As Oliver and Boyd[8] have commented, the lipid effects of moderate doses of estrogen apparently are as great as lipid changes occurring with very large doses.

Summary and conclusions

Study in 16 patients who had received estrogen therapy for at least 3 months without clinical reaction, and who later developed clinical reactions to estrogen therapy in response to increased time and dosage, demonstrates that lipid changes are already maximal before occurrence of breast tenderness and do not become greater with increased time and dosage.

Changes in the serum lipids under estrogen therapy occur to a maximal degree *before* the patients develop any clinical manifestation such as breast tenderness, provided that the initial dose is small and that dosage is increased gradually until some clinical manifestation is evident. Estrogen doses causing no clinical manifestation cause maximal changes in the serum lipids.

References

1. Cohen, W. D., Higano, N., and Robinson, R. W.: Serum Lipid and Estrogenic Effects of Manvene, a New Estrogen Analogue, Circulation **17**:1035-1040, 1958.
2. Eilert, M. L.: Effects of Estrogens Upon Partition of Serum Lipids in Female Patients, Am. Heart J. **38**:472, 1949.
3. Eilert, M. L.: Effect of Estrogens on Partition of Serum Lipids in Female Patients, Metabolism **2**:137-145, 1953.
4. Furman, R. H., Howard, R. P., Norcia, L. N., and Keaty, E. C.: The Influence of Androgens, Estrogens and Related Steroids on Serum Lipids and Lipoproteins, Am. J. Med. **24**:80, 1958.
5. Lowry, O. H., et al.: Quantitative Histochemistry of Brain: Chemical Methods, J. Biol. Chem. **207**:1, 1954.
6. Marmorston, J., Magidson, O., Lewis, J. J., Mehl, J., Moore, F. J., and Bernstein, J.: Effect of Small Doses of Estrogen on Serum Lipids in Female Patients With Myocardial Infarction, New England J. Med. **248**:583-586, 1958.
7. Marmorston, J., Moore, F. J., Magidson, O., Kuzma, O., and Lewis, J. J.: Effects of Long-Term Estrogen Therapy on Serum Cholesterol and Phospholipids in Men With Myocardial Infarction, Ann. Int. Med. **51**:972-982, 1959.
8. Oliver, M. F., and Boyd, G. S.: Influence of Sex Hormones on Circulating Lipids and Lipoproteins in Coronary Sclerosis, Circulation **13**:82-91, 1956.
9. Pearson, S., Stern, E., and McGavack, T. H.: Rapid, Accurate Method for Determination of Total Cholesterol in Serum, Analytical Chem. **25**:813, 1953.
10. Robinson, R. W., Higano, N., Cohen, W. D., Sniffen, R. C., and Shorer, J. W., Jr.: Effects of Estrogen Therapy on Hormonal Functions and Serum Lipids in Men With Coronary Atherosclerosis, Circulation **14**:365, 1956.
11. Russ, E. M., Eder, H. A., and Barr, D. R.: Influence of Gonadal Hormones on Protein-Lipid Relationship in Human Plasma, Am. J. Med. **19**:4-24, 1955.
12. Stamler, J., Pick, R., and Katz, L. N.: Experiences in Assessing Estrogen Antiatherogenesis in Chick, Rabbit and Man, Ann. New York Acad. Sc. **64**:596-619, 1956.
13. Steiner, A., Payson, H., and Kendall, F. E.: Effects of Estrogenic Hormones on Serum Lipids in Patients With Coronary Arteriosclerosis, Circulation **11**:784-788, 1955.

A study of hypnotics in normal subjects with induced awakening

An analysis of the sleep characteristics of normal male subjects who have been given a large volume of water to drink just before retiring shows that sleep is disturbed in a fraction of the group. The hypnotic activity of a standard barbiturate is studied against the background of the sleep disturbance using both subjective and objective criteria. Although both types of criteria reflect the primary pharmacologic action of the drug, each has its own particular advantages and disadvantages which are discussed in the report.

G. A. Condouris, Ph.D., P. J. Costa, M.D., Ph.D., and D. D. Bonnycastle, M.D., Ph.D. *Jersey City, N. J.*
Seton Hall College of Medicine and Dentistry

Repeated attempts have been made to devise clinical experiments for the evaluation of hypnotic drugs which give unequivocal information as to the activity of the drugs in question. Although many successful experiments have been reported, the need for improved experimental designs persists, since many approaches to the solution undoubtedly have not been explored and failures in certain types of studies of hypnotic drugs, such as those with office patients, have been reported.[4] One deterrent to a more rapid progress in development of clinical experiments is, of course, the limitation imposed by the need for subjects meeting certain special requirements for inclusion in clinical investigations. However, a very substantial source of experimental subjects can be found among medical and dental students who could participate in clinical studies either as a part of their medical curriculum, especially in their training in pharmacology, or in studies in which they are paid subjects. The regular availability of these subjects would permit the examination of different experimental designs from which appropriate ones could be applied to actual clinical situations. Goldstein[3] in this country and Isaacs[5] in England have reported success with such a procedure. The results to be presented will indicate the general utility of this approach.

A necessary condition for the proper evaluation of hypnotic drugs is the presence of disturbed sleep in the experimental subject. In the patient with sleeping difficulties, insomnia cannot be expected to occur regularly, therefore, appraisal of hypnotics in such individuals is subject to the vagaries of the physiologic and psychological disturbances which interfere with normal sleep. The present study was designed with the purpose of experimentally

This study was supported in part by grants from Warner-Chilcott Laboratories and Smith, Kline & French Laboratories.

Table I. *Census of participants in the study*

		No. of subjects
Completing full treatment regimen		133
Treatment subdivisions:		
Placebo, secobarbital 50 mg., secobarbital 100 mg.	98	
Placebo, secobarbital 25 mg., secobarbital 50 mg.	35	
Remaining in final analysis		73
Treatment subdivisions:		
Placebo, secobarbital 50 mg., secobarbital 100 mg.	47	
Placebo, secobarbital 25 mg., secobarbital 50 mg.	26	

creating a physiologic condition which sufficiently interferes with the sleep pattern of normal subjects so that full expression of the pharmacologic effect of hypnotic drugs would be permitted. The general experimental approach is based on the technique reported by Isaacs[5] in which a water load given to normal subjects serves as a physiologic stimulus to waking. Hypnotic activity of a drug is then related to the duration of sleeping time under the stress of this water load. A standard well-known barbiturate, secobarbital, was the hypnotic used.

Method

The subjects in the study were male medical and dental students and a small number of members of the faculty. None of the participants had any pre-existing sleep problems.

The experiment was designed as a randomized group design in which each subject received drug treatments in a completely randomized order. This design minimizes the risk of bias caused by systematic environmental factors, which could be a serious problem with a student population, and by drug interactions resulting from a singular or haphazard order of administration. One of the drug treatments, given to all subjects, consisted of capsules containing lactose as the placebo treatment. Since the danger of personal bias on the part of the subject or the investigator was obviated by the "double blind" technique, the response of each subject on placebo treatment served as a base line upon which to analyze the responses to the other treatments.

Each subject received the drugs identifiable only by coded letters and was given written and oral instructions on the physical aspects of the study. They were permitted to eat and drink in their normal manner on an experimental evening which they selected as being typical for them. However, they were to abstain from any additional food or beverage after 9 P.M. Immediately before retiring they were to void, drink 700 ml. of water, take the capsules designated for that evening and record the time. On first awakening, they were to urinate, measure and record the volume, note the time, and estimate the time it took to fall asleep. Additional questions were asked regarding subjective impressions as to the quality of the sleep and the after-effects on awakening. The hypnotic used was secobarbital sodium in doses of 25, 50, and 100 mg.

The size of the water load was a compromise based on the experience of Isaacs[5] with 500 and 1,000 ml. and on a preliminary trial on 10 subjects from our study. Each subject was supplied with two calibrated paper containers, one for the water load and one for measuring the urine volume.

Results

More than 133 subjects started the treatment schedule, but the data of only those who completed all the treatments are included in the analysis. The 133 subjects

meeting this requirement received one of two treatment regimens shown in Table I. The dosages of secobarbital were selected for the purpose of exploring the dose-response curve for this hypnotic. Since 100 mg. of secobarbital is the usual clinical hypnotic dose, and could therefore represent a ceiling dose or a near-ceiling dose, it was decided to examine smaller doses. Each subject was given 2 doses of the hypnotic as well as the placebo. Obviously, the number of treatments given to each subject could have been extended, but this would lessen the chances of selecting relatively homogeneous nights for the test.

A compilation of the sleeping characteristics of the 133 subjects is presented in Fig. 1. The duration of sleep is actually the elapsed time between falling asleep and first awakening. However, since the subjects rather uniformly took less than 30 minutes to fall asleep and since the time to falling asleep is at best an estimate, it was decided to define the duration of sleep as the time between going to bed and first awakening to urinate. It is apparent in the histograms that the magnitude of individual variation is exceedingly large. For example, in the distribution of sleep times on placebo, there is a nineteen fold divergence in sleep duration between the shortest sleep (30 minutes) and the longest sleep (570 minutes). It is also readily seen that the distribution of placebo responses is not normal but has the characteristics of a multimodal distribution. While this latter fact is not obvious in the histograms for the 25 mg., 50 mg., and 100 mg. secobarbital responses, it is clear that in each of these the distribution has a tail in the lower sleep times and has an abrupt cutoff in the upper sleep duration. The asymmetry is most probably a consequence of the inability of the subjects to express fully their max-

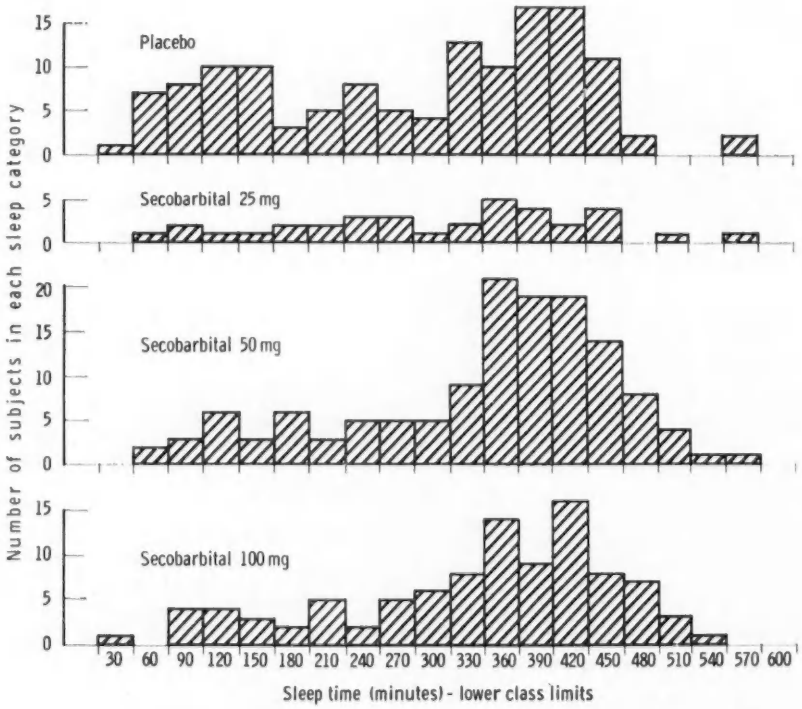


Fig. 1. Distributions of sleep duration experienced by the 133 subjects on different treatment nights. The ordinate gives the frequency with which a given sleep duration was observed; the abscissa defines the sleep time classes expressed by the lower class limit. For example, the 30 minute bar represents the class with boundaries between 30 and 59 minutes, inclusive.

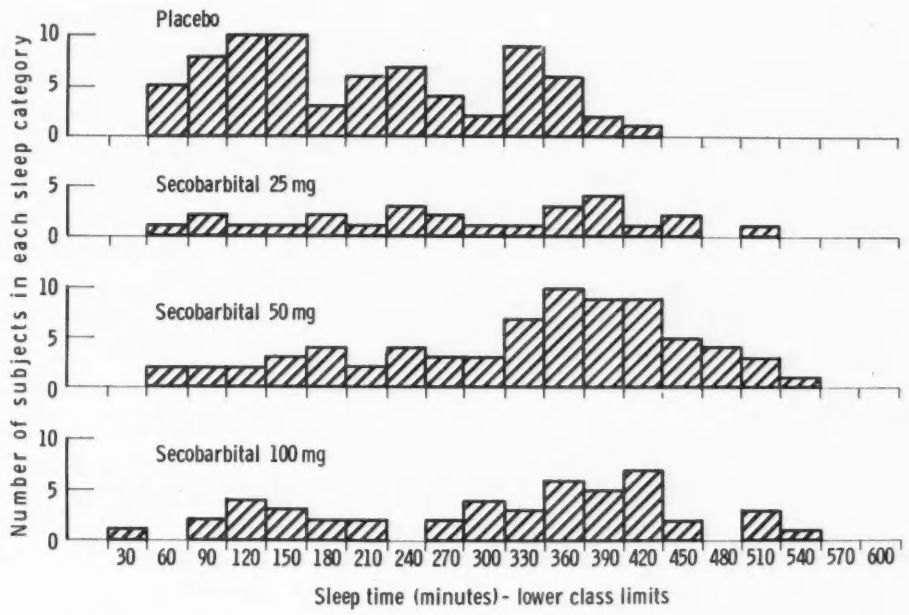


Fig. 2. Distributions of sleep duration experienced by the final 73 subjects. Same conditions as in Fig. 1.

imum sleep potential because of the interventions of an artificial awakening device—the alarm clock.

Regardless of the aberrant forms of all the distributions in Fig. 1, the tendency of the barbiturate to prolong sleep time at all dose levels is to be found in the shift of the densities of the distributions to the right when compared with the placebo sleep pattern. The obvious non-normality of these distributions precludes the application of conventional statistical tests of significance. Therefore, an analysis of these results should be made on pharmacologic grounds in order to make the data more amenable to statistical consideration.

A comparison of the individual data on the sleep durations of the 133 subjects on placebo nights with the statement supplied by each subject as to his normal sleep duration without medication on a water load showed that many subjects experienced no sleep difficulties with the water load. That is, these individuals slept approximately as long as on a regular non-experimental night. It was arbitrarily decided that anyone who slept his regular sleep duration or who slept to within one hour of his regular sleep duration could not be considered as having a sleep problem and therefore would not be expected to show any prolongation of sleep when testing a hypnotic. Furthermore, if a subject awoke in less than 60 minutes after retiring on a placebo night, he was also rejected as a candidate because the stimulus intensity was so severe that a hypnotic drug might not have time to develop its effect before the subject awoke. Fifty-nine met the criteria for the former category and one fit the latter criterion. Together they represent 45 per cent of the original population, leaving 73 subjects who were suitable for entering into a final analysis.

The sleep patterns of the new sample under the effects of placebo and the various secobarbital doses (Table I) are illustrated in Fig. 2. Examination of the placebo histogram reveals that the density of subjects in the upper limit of sleep duration has been diminished as would be expected. The distribution is still skewed as are the distributions of the barbiturate histograms below. Apparently, the factor resulting in a truncation of the sleep times is still operating. Note that the densities in the barbitu-

rate histograms are shifted to the right relative to the placebo distribution. The tendency toward prolongation of sleep by the secobarbital is therefore still present in this new sample. It appears that the 50 mg. distribution is essentially normal; however, a graphic analysis for normality using the probit test[1]* suggests that the distribution is comprised of two fused normal populations. Once again the decision was made not to compare the mean sleep times on each of the 4 treatments with a conventional test such as the t test.

It is a common experience to find that, when given sets of raw data are not in themselves normally distributed, differences between 2 observations made on the same experimental unit would describe a Gaussian curve. Therefore, for a more discriminating method of analysis, advantage was taken of the experimental design which permitted comparisons between treatments within each subject. The differences in duration of sleep with any 2 treatments were then averaged over all subjects entering the comparison to arrive at a mean difference in duration. Because the number of differences in the 25 mg. secobarbital sample was less than 30, the presence of normality was tested by plotting the rankit[1] against the difference in sleep duration (Fig. 3). On the other hand, the plot of the probit against the sleep time difference was used to test normality in the placebo vs. secobarbital 50 mg. and the placebo vs. secobarbital 100 mg. contrasts. The linearity of each curve in Fig. 3 leads to the decision that the differences in the 3 contrasts of sleep time are samples of normal popula-

*The probit test for normality as well as the rankit test for samples with less than 30 observations provide a graphic means for making a decision as to whether or not the sample was drawn from a normal (Gaussian) population. Although these tests cannot actually prove the presence of normality, they can be used to determine the extent of departure and whether such a departure is systematic or random, thus allowing the investigator a certain amount of confidence (not expressible in numerical terms) to base his decision on using tests of significance derived from a Gaussian distribution.

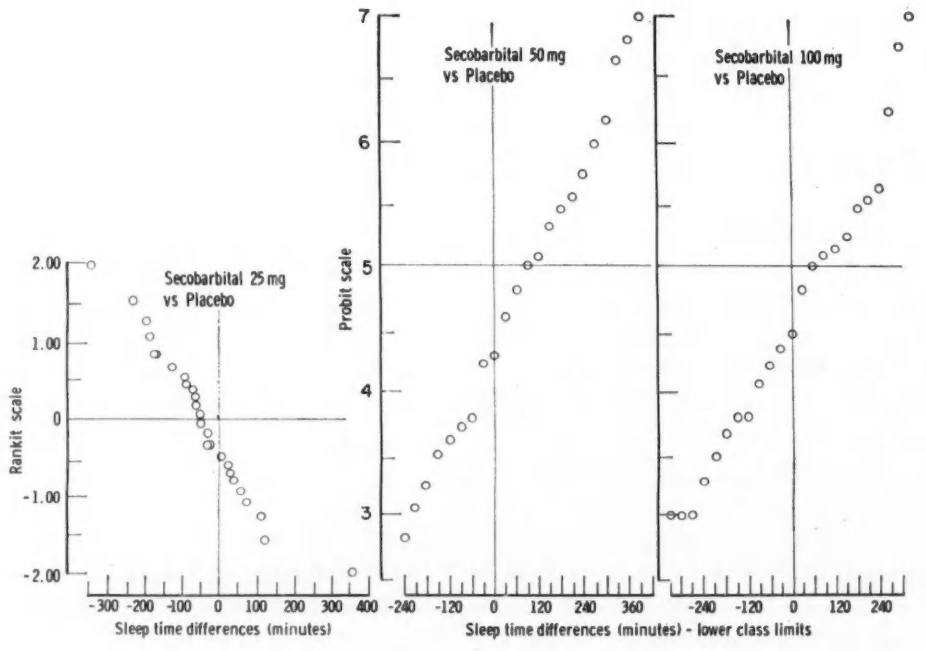


Fig. 3. A graphic test of normality of the intrasubject sleep-time differences. The rankit test was used for the secobarbital 25 mg. versus placebo differences, the probit test for the other two contrasts. In each instance, the sleep duration on placebo night was subtracted from the sleep duration from the same subject on the drug night.

Table II. *Results of tests of significance on the sleep durations*

*Drug comparison**	*No. of individual comparisons*	*Mean difference in comparison (minutes)*	*S.E. of difference (minutes)*	*Student's t test*	*P value*
Secobarbital 25 mg. vs. placebo	26	+67	±27	2.48	0.02
Secobarbital 50 mg. vs. placebo	73	+126	±18	7.00	<0.001
Secobarbital 100 mg. vs. placebo	47	+110	±24	4.58	<0.001

*The unit of comparison is the difference in sleep duration derived by subtracting the sleep duration on placebo night from the sleep duration on drug night for each subject.

Table III. *The incidence of subjective effects reported by subjects for each treatment*

Subjective effect	*Placebo*	*Secobarbital 25 mg.*	*Placebo*	*Secobarbital 50 mg.*	*Placebo*	*Secobarbital 100 mg.*
Quality of sleep:						
Good	18	22	46*	66	28†	42
Fair to poor	8	4	27	7	19	5
Morning drowsiness:						
None	22	16	64	55	42†	32
Mild to severe	4	10	9	18	5	15
Morning headache:						
None	24	22	67	66	43	43
Mild to severe	2	4	6	7	4	4
Gastrointestinal distress:						
None	24	24	68	70	44	47
Mild to severe	2	2	5	3	3	0

*P determined from χ^2 test of 2 × 2 contingency table is less than 0.001.
†P determined from χ^2 test of 2 × 2 contingency table is between 0.05 and 0.01.

tions, therefore, the t test may be applied to determine statistical significance of the 3 mean differences. The results of the tests of significance are summarized in Table II. The subjects were able to distinguish all doses of secobarbital from the placebo. The average increase in sleep time was about 1 hour with the 25 mg. dose and about 2 hours with the 50 and 100 mg. doses. Although numerically the mean difference in sleep time for the 50 mg. dose is greater than for the 100 mg. dose, the difference is not statistically significant. Furthermore, there is no statistical significance between the mean sleep difference on the 25 mg. dose of secobarbital and the mean sleep difference on 50 mg. secobarbital (P is greater than 0.05).

A group consisting of 13 subjects was presented with nothing but placebo capsules in a double blind manner on each of 3 experimental nights in order to explore the variations that may occur by chance alone in repeated tests in a given subject. It was found that the mean sleep duration on the first night was less by approximately 1¼ hours than the duration of sleep on the 2 subsequent nights. The mean sleep durations on nights 1, 2, and 3 were, respectively, 282, 354, and 360 minutes. The shorter sleep duration on the first night may be a reflection of the subjects' zeal in con-

ducting the experiment. Had the treatments not been randomized in the main study the validity of the results would have been seriously impaired by this effect.

The results of the subjective appraisals of the treatments are presented in Table III. The frequencies of occurrence of the various subjective qualities are stated in the body of the table. The 4 observed frequencies for each treatment comparison and each subjective quality were analyzed as a 2×2 contingency table using the χ^2 test.[1] Only 3 contingency tables showed significant differences. Under the stress of the water load, 37 per cent of the subjects complained of a fair to poor night's sleep when taking placebo capsules whereas only 10 per cent made this complaint on the nights they had taken the 50 mg. dose of secobarbital. On this same quality, 40 per cent of the subjects experienced fair to poor sleep on the placebo while in the same experimental group only 11 per cent reported this quality on the secobarbital 100 mg. night. The subjects evaluating the 100 mg. dose of the barbiturate were also able to distinguish the difference between the placebo and the barbiturate on the basis of the presence or absence of drowsiness in the morning.

Examination of the urine volumes recorded in Table IV shows no difference in the mean urine output from each treatment either in the original sample of subjects or in the sample used in the final analysis. The largest difference in urine output in either Table IV A or B was 30 ml. which is just about the accuracy of measurement. There was no correlation between the volume of voided urine and the duration of sleep.

The effects of body weight and body surface area on both urine output and duration of sleep on barbiturate nights were examined in an additional sample of 15 subjects and were found to be unrelated.

Discussion

The evidence provided by the experimental method used in this study shows that sleeping patterns of normal male subjects can be deranged by presenting the subjects with a physiologic stimulus in the nature of a heavy water load at bedtime. Furthermore, with appropriate statistical management of the data on sleep duration, it was found that the subjects were able to distinguish the hypnotic activity of 3 dosages of secobarbital from placebo. Certain qualifications have to be made in the results and conclusions in order that the scope and limitations of the findings may be properly framed.

The 700 ml. water load did not have an adverse effect on the sleep of all the 133 subjects who entered the study; 50 of the 132 subjects who slept more than 1 hour on placebo, i.e., 45 per cent, also slept to

Table IV. *Urine output on first awakening*

Drugs	*No. of subjects*	*Mean urine output (ml.)*	*Range (ml.)*
A. ORIGINAL SAMPLE.			
Placebo	133	569	150 to 1,200
Secobarbital 25 mg.	35	570	200 to 1,150
Secobarbital 50 mg.	133	539	150 to 1,200
Secobarbital 100 mg.	98	539	175 to 1,050
B. FINAL SAMPLE.			
Placebo	73	576	175 to 1,200
Secobarbital 25 mg.	26	580	250 to 1,150
Secobarbital 50 mg.	73	583	150 to 1,200
Secobarbital 100 mg.	47	590	175 to 1,025

within 1 hour of their usual sleep durations on the placebo night. Obviously, then, the intensity of the stimulus from the urinary bladder was either insufficient to awaken these subjects, or the subjects were experiencing a bona fide hypnotic effect from the placebo. The former reason seems more probable and could be further explained by the possibilities that these subjects either had high thresholds for perception of stimuli from the full bladder or did not excrete a sufficient volume of urine to evoke an awakening stimulus. The latter point is not likely judging from the facts presented in Table IV which show that the subjects who had a full night's sleep on placebo excreted no less urine than the subjects with interrupted sleep. In addition, Homer Smith[7] has found that normal subjects are able to clear even a 1 L. oral water load within 2 hours. To have attempted to force the high-threshold group into the disturbed-sleep category by increasing the water load on all subjects would undoubtedly have led to the loss of subjects who would either awaken too early or who would experience noxious effects from a larger water volume. Regardless of the causes, the failure of this group to react to the water load constituted a real threat to the unbiased success of the experiment because they exhibited no condition which could be relieved by legitimate hypnotics. Removal of all their data without a priori examination of their responses to the barbiturate seems to have been well within the realm of proper logic and would avoid any systematic bias. In fact, this technique is analogous to the usual technique for selection of clinical patients for hypnotic studies in which only those hospital patients who complain of insomnia are included.

Having thus eliminated those who have the potential of sleeping a full night without the intervention of a hypnotic drug, a new sample of subjects was obtained. An examination of the sleep time distributions of these subjects on the 4 treatments again revealed the presence of skewed normal or multimodal normal distributions as was evident in the distributions of the original sample. To adapt standard tests of significance, such has the t test, to the mean sleep duration on each treatment in the face of non-normality is fraught with the danger of violating certain of the assumptions underlying the tests. Not only the truncation of the sleep times at the upper ranges with the rather prominent skewing of the distributions but also the contamination of the sample with subsamples requires special corrective techniques which are not simple to execute or necessarily desirable to invoke. With wisdom, the renowned pharmacologist A. J. Clark[2] said, regarding mathematical management of biologic data, "It must be remembered that a formula is merely a form of shorthand which is convenient but nevertheless dangerous because it may conceal widely improbable assumptions which would at once be rejected if stated in words."

The cross-over experimental design used in the study obviated any complications in interpretation of the data since the within-subject sleep differences, which were normally distributed, could be used as the unit of measure. Although the barbiturate was found to increase the duration of sleep in all the dosages used, no dose-response curve was in evidence. This is an interesting development because it implies that an equivalent prolongation of sleep could be obtained with doses ordinarily not considered as hypnotic. The lower level of significance in the 25 mg. secobarbital versus placebo contrast suggests that investigation of dosages between 25 and 100 mg. might lead to a dose-response curve.

Although Isaacs developed the experimental technique for disturbing sleep, his analysis of the results differs from that presented here. His major objective was to extract a depth of sleep index from each subject on each treatment. He defined the index as: $D = (\log t) \times (\log v)$.

This empirical equation was obtained on the assumption that sleep associated with

large urine volumes is deeper than sleep with small urine volumes on awakening. His own critical analysis of the index showed that D was not related to v and that D was dependent on t only when the sleep duration was less than 3½ hours. Furthermore, he pointed out that the index could give erroneous estimates of depth of sleep under certain conditions. Our results show that the duration of sleep was not correlated with the awakening urine volume and we hesitate to use Isaacs' mathematical expression of depth of sleep because it implies a perfect relationship between the expression $(\log t) \times (\log v)$ and the depth since the coefficient of this expression is unity. In addition, use of this equation with its complex unitage *(log minutes) (log milliliters)* obscures the information on the actual duration of sleep or on the differences in duration of sleep on drug and placebo nights.

Although the urine output data were not utilized in our study to determine the sleep characteristics, their collection serves as an internal control of the diuretic or antidiuretic actions of potential hynotic agents.

It is interesting that the analysis of the subjective data leads to the conclusion that the subjects could distinguish the placebo capsules from the secobarbital 50 mg. and 100 mg. doses when they were asked to appraise the quality of sleep on treatment nights. This often-used criterion seems to be better suited than the question of the presence or absence of morning "hangover." In spite of the success of the subjective appraisal of treatment effects, its utility is limited by its low sensitivity, e.g., the subjects could not discern any difference between placebo and a 25 mg. dose of secobarbital, and by its failure to give any indication of graded effects on sleep time. The superiority of the objective method on these two factors is readily appreciated from the results presented in this study. On the other hand, a disadvantage of the use of sleep duration as the criterion of hypnotic activity is the necessary assumption that the subject first awakens only when he rises to urinate. It does not account for interrupted sleep or periods of wakefulness prior to arising to void; therefore, an additional criterion such as the subjective report on the quality of sleep or on an objective appraisal of the presence of wakeful periods in hospitalized subjects would be of value. Lasagna[6] reports on such a method for testing hypnotics in ward patients.

The facts obtained in this experiment suggest certain factors that should be considered in actual clinical trials of hypnotic drugs. First, it is mandatory that the data be examined for distribution characteristics in order to avoid invalid conclusions stemming from the misapplication of statistical methods. Second, in the selection of dosages of standard hypnotic agents or even new drugs, the dosage range usually considered as a sedative range should be explored since it is possible that the current recommended dose may be higher than necessary. Third, the well-established yet often-neglected need for randomization of drug treatments and use of the double blind technique must be more vigorously emphasized in the design of clinical experiments. Finally, the use of subjective appraisals of drug effects should not be abandoned when objective measurements are used because the subjects themselves can often provide information about a drug that cannot be obtained by any objective technique.

Conclusions

1. A 700 ml. water load given to normal male subjects at bedtime creates a disturbance of sleep in 55 per cent of the individuals. This group can be used to evaluate hypnotic drugs.

2. Secobarbital in dosages of 25, 50, and 100 mg. will prolong the sleep duration in this group relative to that obtained with placebo treatment.

3. Secobarbital in dosages of 50 and 100 mg. can be distinguished from placebo when the criterion for good sleep is based on subjective appraisal.

4. Both subjective and objective measurements should be used in the evaluation of hypnotic activity.

References

1. Bliss, C. I., and Calhoun, D. W.: An Outline of Biometry, New Haven, Conn., 1954, Yale Co-Operative Corporation.
2. Clark, A. J.: General Pharmacology in Hefter, A., Heubner, W., and Schüller, J., editors: Handbuch der Experimentellen Pharmakologie, Berlin, 1937, Julius Springer, Band IV.
3. Goldstein, A.: A Pharmacology Teaching Exercise With Barbiturates, J. M. Educ. **28**:48-50, 1953.
4. Greiner, T., Gold, H., Warshaw, L., Otto, H., and Rinzler, S.: Comparison of Hypnotic Agents in Patients With Insomnia, J. Pharmacol. & Exper. Therap. **116**:24-25, 1956.
5. Isaacs, B.: A Method for Evaluation of Hypnotic Drugs, Lancet **1**:556-558, 1957.
6. Lasagna, L.: A Comparison of Hypnotic Agents, J. Pharmacol. & Exper. Therap. **111**:9-20, 1954.
7. Smith, H. W.: Principles of Renal Physiology, New York, 1956, Oxford University Press.

The history of natural science shows that initially attempts were made, analogous to mathematics, to find an explanation apart from any experience, based on thinking only, i.e., an explanation a priori. This has become a complete failure and it is now an established fact that any and every conclusion based on reasoning should be verified, in natural science, by observation, preferably by observations made in experiments. In medicine this fact has not been generally accepted so far. Farsighted minds such as John Hunter were aware of this long ago, as shown by Hunter's famous exclamation of impatience: "Why think? Why not try the experiment?" with which he addressed his friend and pupil Jenner.

From "Critical Evaluation of the Efficacy of New Drugs" by J. H. Pannekoek, Postgraduate Medical Journal, Vol. 33, 1957.

The anabolic steroids

The existence of underdeveloped and debilitated patients as well as the widespread use of drugs with catabolic effects makes it essential that a nontoxic, nonandrogenic, highly potent anabolic drug be developed. Some of the more significant historical, experimental, and clinical aspects of the anabolic steroids are discussed. Before their wide therapeutic acceptance, further critical evaluation of these drugs will be necessary.

Peter H. Berczeller, M.D., and Herbert S. Kupperman, M.D., Ph.D.
New York, N. Y.
Department of Therapeutics, New York University Medical Center

Medicine has long sought a specific chemical compound that would be effective in repairing and augmenting the protein components and supportive structures of the body. The need for such agents is obvious. With the advent of the clinical use of the sex steroids, it appeared that fulfillment of the hope for the ideal anabolic steroid could be anticipated. Despite the passage of three decades since the original steroids appeared on the medical horizon, however, a universally acceptable anabolic agent without untoward side effects has yet to be developed.

By anabolism we mean "a constructive metabolism indicating the building or formation of tissues in general."[1] This process is dependent upon general good health, adequate and balanced diet, physical activity, and the presence and action of the anabolic steroids and growth hormone, the former occurring as estrogens and androgens in both males and females.

There are a number of clinical conditions in which the use of anabolic agents is desirable. This is particularly the case when endogenous anabolic steroids are not adequate to maintain anabolism or when endogenous production of anabolic steroids is absent. The agonadal state, due to either disease, operation, or idiopathic causes, is the most obvious indication for such therapy. The process of aging with its attendant decline in steroid production and the resulting muscle wasting, loss of energy, and osteoporosis is another example of the need for anabolism. The postoperative patient is subjected to profound catabolic processes and will often require anabolic therapy, particularly when the patient is debilitated and in constantly negative protein balance. The chronic administration of corticosteroids frequently requires the use of anabolic agents to offset the osteoporotic and myopathic effects that may accompany this mode of therapy. And, finally, retarded growth in children may be considered as an indication for the use of these steroids, provided no adverse effects are expected.

This paper will consider estrogen, testosterone, methyltestosterone, methylandro-

stenediol, norethandrolone, and nandrolone phenpropionate, purely as anabolic agents. Their use in other modalities of therapy is beyond the scope of this paper and will not be discussed here.

Chemistry. It might be well at this point to review briefly the basic chemistry of the substances under discussion.

As can be seen (Fig. 1), the 4 ring nucleus is common to all. Considering the far-reaching differences in the actions of these substances, their chemical differences are relatively small. For example, the difference between testosterone and 17-ENT is that the latter has no C-19 methyl group and that its 17-alpha hydrogen is substituted by an ethyl group. Yet, this change has a profound effect on the virilizing potential, as will be expanded upon below. On the other hand, studies have shown that when the 17 position contains more than two carbons, both the anabolic and androgenic activity is usually reduced.[1] The converse is also true. Other studies have shown that one can prolong the action of the 19-norsteroid by adding a phenylpropionate group at the 17-beta position.[2] Other 19-norsteroids closely allied chemically to those under discussion have a primarily progestational effect at much lower doses than would be necessary to achieve a primarily anabolic effect.

Testosterone

Assay. The assay of the androgenic anabolic drugs is of some interest. This has followed two lines of thought. One is the nitrogen-retaining technique ascertained by balance studies first proposed by Kochakian and Murlin[3] in 1935. This, of course, is more feasible in humans in whom weight and height determination as well as calcium and nitrogen balance studies have been of great importance in determining the clinical efficacy of the anabolic drugs. In animals, the observation that testosterone propionate (TP) caused definite hypertrophy of the temporal muscles of the guinea

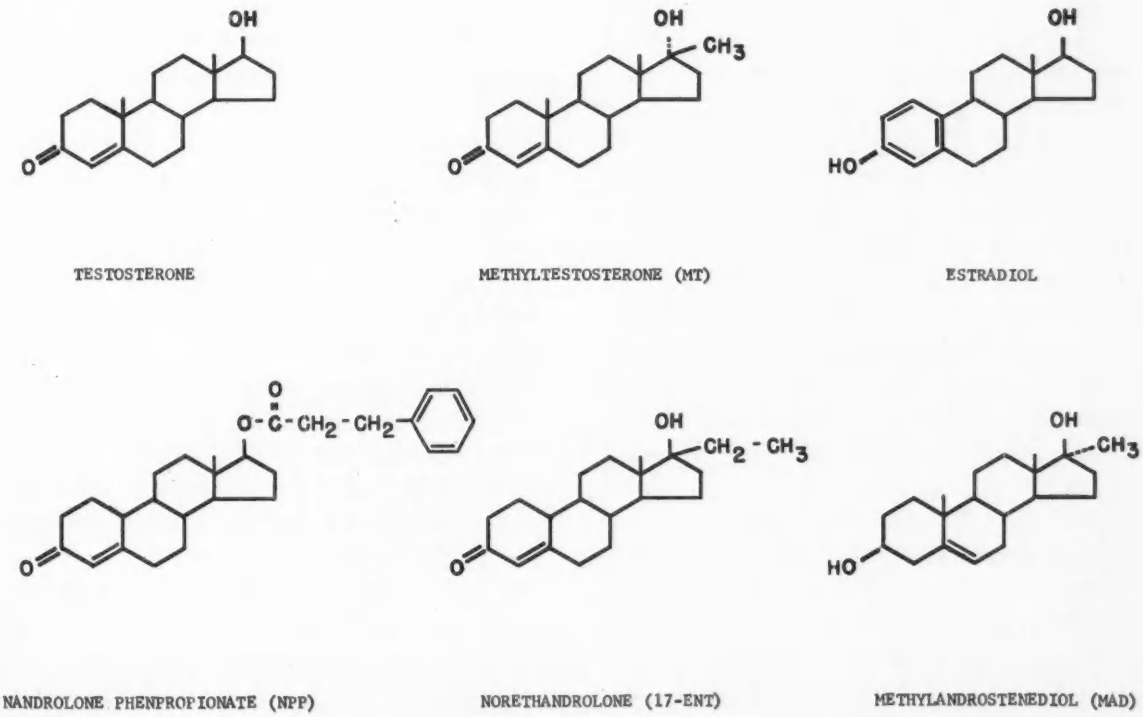


Fig. 1.

pig[4] was the forerunner of the levator ani method which, despite some objections,[5] is well accepted at this time. The latter technique has as its basis the increase in weight of the levator ani muscle of the castrated male rat.[6,7] Its advantage is accessibility of the muscle, clear demarcation of end point, and the quantitative response of this muscle to graded doses of steroids. Androgenicity has been measured, on the other hand, by such methods as estimation of axillary hair growth,[8] increased libido, acne, and 17-ketosteroid excretion in the human, and increase in size of the seminal vesicle and ventral prostate in animals. There are also some highly specific anabolic effects attributed to testosterone. These include the growth of the comb, wattles, and ear lobes of the castrated cockrel (and growth of the comb in the hen), renal enlargement caused by testosterone administration,[9] the myometriotrophic effect which has also been reported,[10] as well as the anabolic effect on the protein matrix of the skin.[11]

The generally greater muscle development and usually greater height and weight of postpubertal males as compared to females point to the anabolic nature of the androgenic steroids. The softening of the toughened meat of male animals by castration offers practical evidence of the anabolic nature of endogenous testosterone.

Experimental aspects. Experimental data on the anabolic properties of testosterone are extensive. Kochakian and Murlin[3] extracted male hormone from urine and injected it into castrate dogs. They found that there was a drop in urinary nitrogen, which began the first day after injection and reached a maximum within 5 days, with a rise in urinary nitrogen following cessation of injections.

The anabolic effect of androgens was demonstrated in the normal, castrated, adrenalectomized, hypophysectomized, and diabetic male rat and in the normal and ovariectomized female rat.[12] Similarly anabolism was also shown in the thiouracil-treated and surgically hypothyroid castrated rat. In contrast to this, TP was found to decrease the body weight of normal adult rats in proportion to the dose administered. The loss in body weight was thought to be due primarily to a diminution of fat in the subcutaneous and abdominal areas with an associated decreased appetite. The protein content of the skin in these animals was found to be markedly decreased. In young, growing, adult rats, TP decreased the rate of growth but not sufficiently to decrease the body weight. However, cessation of androgen administration in both young and old normal rats resulted in an increase in appetite with a rapid restoration of body weight.[13]

The discrepancy in the above results, showing the anabolic effects of the androgen on specific muscles on the one hand, with loss of body weight and decrease in protein matrix of the skin on the other, may be due to overdosage of testosterone with resulting toxicity in the latter studies.

The so-called "wearing-off" effect of testosterone is of interest. It has been found that the initial ability of androgens to cause nitrogen retention disappears on continuation of the injections, with a resulting loss in the body weight that had been gained.[14] The "wearing-off" effect of the androgen on body weight and nitrogen retention may be postponed by increasing the dose, something which has also been seen in the case of growth hormone. For example, when normal rats were kept on a dose of 0.25 mg. of TP daily, the total nitrogen retention for a 21 day period was 312 mg. with a gradual rise in daily nitrogen excretion. However, when the dose was increased to 2.5 mg. a day, postponing the return of the nitrogen balance to equilibrium, a further retention of 173 mg. of nitrogen over a 14 day period was effected, with another temporary fall in urinary nitrogen being observed.[15]

The etiology of the "wearing-off" effect is not clear. It is not due to the inhibitory effect of the exogenously administered hormone on the release of the anabolic principle of the anterior pituitary or adrenal cortex because these same effects can be pro-

duced in hypophysectomized and adrenalectomized rats. It is also not due to antihormone formation since an anabolic effect can be repeatedly demonstrated in the same rat.[14]

Attempts at defining the exact nature of the effect of TP on the muscle have been made. In castrated adult rats injected with TP, protein was found to be deposited in the following order of decreasing magnitude: carcass, seminal vesicles and prostate, and liver and kidneys. If the intensity of therapy was increased by either prolonging the duration or increasing the dosage, the carcass began to lose not only fat but also protein, which was apparently diverted to accessory sexual organs and, to a smaller extent, to the kidneys. It was also found that the amino acid composition of skeletal muscle, liver, kidney, seminal vesicles and prostate was not changed by the androgen.[16]

The biochemical effect of testosterone was studied in the levator ani muscles of 21- and 54-day-old rats for 1, 3, 5, and 7 days. Initially, striking increases in glycogen concentration were found to occur. With continued testosterone therapy, a decrease in glycogen concentration was associated with rapid growth of the muscle. These changes in total glycogen were due to the trichloracetic acid soluble moiety, while acid insoluble glycogen remained unchanged. It is therefore thought that the action of testosterone may be mediated via a primary effect on the energy aspects of muscle metabolism and that the mechanisms involved in protein synthesis may be accelerated when extra energy is made available in the form of increased trichloracetic acid soluble glycogen levels.[17] It has also been found that TP gives only a transitory fall in nitrogen excretion in rats kept on protein-free food for a short time, but fails to do this entirely in rats which have already been kept on protein-free food for 2 weeks prior to TP administration. In contrast to growth hormone, TP fails to decrease the amino acid content of blood in freshly eviscerated rats and does not cause inhibition of liver arginase.[18]

Diet also influenced the response of castrate dogs as far as nitrogen-retaining activity was concerned, particularly when nitrogen intake was maintained above minimal levels. At the minimal level of nitrogen intake, no evidence of retention of nitrogen could be demonstrated.[19]

Clinical application. Since the anabolic effects of androgenic hormones have been discovered, the clinical use of these substances has been widespread. However, the obvious undesirable effects of the androgens upon hirsutism, acne, secondary sexual characteristics, and menstruation have provided the impetus for development of analogues of testosterone which would show a dichotomy between anabolism and androgenicity. The virilizing effect of all androgenic steroids and their analogues has been most disturbing, since their chronic use in adequate doses will produce sexual precocity, unsightly body hair, and disturbing increase in libido. The 19-nor analogues appear to cause less of the latter and will be discussed below. At any rate, testosterone is an anabolic drug par excellence, and an understanding of its effects is necessary for adequate comprehension of anabolism in general.

One of the first significant clinical studies on the effect of TP was performed in 1938 by Kenyon and associates.[20] They found that daily intramuscular administration of 25 mg. of TP caused a consistent decrease in urinary nitrogen varying from 1.16 to 4.51 Gm. of nitrogen daily in each of four eunuchoid patients studied. Also, there was a decrease in urinary sodium. The authors came to the conclusion that the gain in weight was largely due to fluid retention. Later, in 1944, they[21] felt that there must be an increase in the mass of nongenital tissue in individuals who are on TP therapy, because of the marked retention of inorganic phosphorus, sulfate, and potassium. Wilkins and Fleischmann[22] believe that the increase in body weight resulting from androgen therapy is due to both building of protein tissues and fluid retention. In the light of our present-day knowledge

of the pharmacologic effect of the doses used by both Kenyon's and Wilkins' groups, we feel that the increase in weight due to androgen therapy in the above studies was most probably secondary to protein anabolism alone.

The indications for testosterone therapy have been many and varied. It has been used in the treatment of premature infants and developmentally retarded children. In one study, 15 premature infants of both sexes weighing less than 2,000 grams (with a predicted mortality rate of approximately 50 per cent) were given 2.5 mg. of methyltestosterone (MT) twice daily for from 4 to 7 weeks. All 15 survived. Weight and increased vigor were initiated early, each child gaining at least 1,000 grams during the treatment period.[23] In children with retarded growth, MT was found to be a potent agent in improving the ultimate height of 2 children, one a boy with mild achondroplasia, the other a girl with Turner's syndrome. Before treatment, the boy, who was 10 years old, was 110 cm. tall with a markedly retarded bone age. After 2 years of MT therapy (5 to 10 mg. daily sublingually), the bone age of the epiphyses increased from 7 to 9 years and his height increased 11 cm. The girl, who was 14 years of age, had a retardation of bone age of about 3 years (an unusual finding in Turner's syndrome) and was 134 cm. tall. After 5 to 10 mg. of sublingual MT daily for 2 years, the height had increased 11.5 cm. whereas the bone age had advanced only from 10 years, 10 months, to about 13 years. These data indicate that, in the described studies, testosterone caused promotion of growth without undue acceleration of skeletal maturation.[24]

On the other hand, Sobel and co-workers[25] believe that testosterone stimulates both linear growth and skeletal maturation. They evaluated the relative influence of oral MT (5 to 40 mg. daily) in 27 children, aged 5½ to 10 years, who were growing slowly. A dose of 5 mg. daily evoked a growth response in the 6 months of therapy, as did larger doses. They found that the average increase in skeletal age was greater than that in height age during the period of therapy. Skeletal maturation continued to advance to a greater degree than had been noted during the control period of observation. Growth increments were found to revert to average normal when therapy was discontinued. The authors conclude, "Since growth is essentially ended when epiphyseal maturation is complete, the observations suggest that testosterone may not be a suitable agent for the promotion of growth." This statement is open to question, however, since, as the authors themselves admit, "there is considerable natural variation in the rate of skeletal maturation and the number of children in each group was small." Moreover, the children were used as their own controls (in the pretreatment period), and a significant evaluation of testosterone in this light would have to be based on the skeletal maturation rate of large numbers of underdeveloped, untreated children. In this regard, Kenyon and his collaborators[21] felt also that maturation of bony structures occurs on testosterone therapy but closure of the epiphyses is not readily induced and, presumably, requires more prolonged therapy with larger doses. Our data with other steroids discussed below disagree with Sobel's conclusion in that we have seen a significant increase in linear growth without notable effects upon accelerating epiphyseal closure.

Other uses of testosterone have included the treatment of patients following total gastrectomy. In these cases, weight loss and negative nitrogen balance are problems of great importance. Van Wayjen and coworkers[26] found that protein utilization in all but one male after gastrectomy was improved following administration of TP. Nitrogen balance in a femal agastric patient was likewise improved as a result of this therapy. This was achieved at a lower dose than necessary for males and was combined with estrogen therapy. When the androgen-treated series was compared with untreated agastric controls, the for-

mer group showed a marked increase in body weight.

Testosterone has been used as a nitrogen-sparing agent after spinal cord injury.[27] The study included 15 patients with spinal cord injuries who were placed on daily doses of 50 to 100 mg. TP intramuscularly. There were 15 untreated controls. The patients on TP showed an initial relative hypoproteinemia despite the induced nitrogen retention. They showed considerably less urinary excretion of nitrogen and creatine, a more favorable status of nitrogen balance, and a lower incidence of decubitus ulcer formation. The hypoproteinemia in the long run, however, was found to be less pronounced than in the untreated controls.

It is now a well-known fact that many of the clinical manifestations of Cushing's syndrome are due to protein loss secondary to corticoid-induced catabolism. These include osteoporosis, striae, and myopathy. With the use of TP (25 to 50 mg. daily), in 3 cases of Cushing's syndrome, Albright, Parson, and Bloomberg[28] found that there was a 20 Gm. retention of nitrogen in 5 days, a prompt retention of phosphorus, decreased urinary calcium, and a marked increase in strength and weight. Despite the modern trend toward the surgical and/or radiation therapy of Cushing's syndrome, it may be well to keep in mind the use of adjuvant protein-sparing therapy for the pre- and postoperative periods when protein catabolism still plays an important role in the patient's symptomatology. It may also be stated at this time that the use of testosterone or its analogues is certainly indicated to combat the serious side effects such as osteoporosis and muscle weakness and wasting noted after the therapeutic application of large doses of corticoids. These are, admittedly, usually factors in long-term, high-dosage therapy, but they may force cessation or drastic reduction in dosage if no anticatabolic agent is employed.

Testosterone has also been used in the treatment of a patient with Addison's disease as well as moniliasis and hypoparathyroidism. Administration produced a gain in weight, decreased urinary excretion of nitrogen, potassium, and sodium, and a marked decrease in serum potassium.[29] The decrease in potassium is probably not due to a corticoid-like effect but may be ascribed to the incorporation of potassium into muscle due to the anabolic effect of testosterone.

In metabolic studies in myxedema following daily administration of 100 mcg. of *l*-triiodothyronine, one patient (a male) showed marked weight loss and a negative nitrogen balance which lasted between 200 and 220 days. Similar changes occurred in a myxedematous female who weighed less than the male but they were neither as marked nor of such long duration. In the male, administration of 25 mg. of TP caused nitrogen retention during the period of negative nitrogen balance. In contrast to the myxedematous patients, daily oral administration of 100 mg. of *l*-triiodothyronine for 10 days to a healthy male volunteer produced insignificant changes in the nitrogen balance and no decrease in weight.[30]

Administration. The oral application of testosterone has been relatively ineffective (as contrasted with that of MT, which is not destroyed when given orally). The ingested steroid is usually rapidly metabolized by the liver or poorly absorbed and excreted via the intestines so that it is only one tenth or one thirtieth as active as when given parenterally.[31,32] Poor absorption probably plays an insignificant role since our own data on the use of oral testosterone indicate a higher 17-ketosteroid level than after equivalent doses of the parenteral medication.[33] The poor therapeutic effect noted after oral administration of testosterone or TP is more probably due to rapid destruction of the steroid by passage through the liver. Methylation prevents the complete destruction of the administered steroid.

On the other hand, esterification of parenteral testosterone causes prolongation

of action and enhances the anabolic and androgenic activities of the steroid. This illustrates a basic principle in endocrinology in that slow release and continuous activity of hormone preparations lead to enhanced effects, in contrast to the rise and fall of stimulation seen with shorter-acting preparations. By use of the growth of the male accessory glands of castrated rats for the quantitation of the effectiveness of various androgens, it was found in one study that both testosterone cyclopentylpropionate and testosterone phenylacetate proved to be the most effective of the long-acting steroid ester combinations. Next in order of decreasing activity were testosterone isobutyrate, testosterone as an aqueous phosphate suspension, TP as an aqeuous suspension, testosterone as an aqueous suspension, TP in oil, and, the least active, testosterone in oil.[33]

It should be noted that while TP as an aqueous suspension gave prolonged effects in animals, it was not applicable to human studies, because of the severe pain it caused at the site of injection.

Another group studied testosterone, testosterone with aluminum phosphate, testosterone cyclopentylpropionate, methylandrostenediol (MAD), and MAD with aluminum phosphate. They found that testosterone cyclopentylpropionate had the best anabolic and androgenic efficacy of all the steroids studied. This was thought to be due to delayed inactivation of the ester. While aluminum phosphate was found to delay the onset and decline of the anabolic and androgenic actions of testosterone in aqueous suspension, it had no such effect on the activity of MAD.[34]

Intravenously administered testosterone appears to be so rapidly metabolized that there is little or no effect as far as the usual modalities of activity are concerned. In one study,[35] 19 subjects were given 240 mg. of testosterone intravenously in human serum albumin solution over a half-hour period. No effect on nitrogen balance was noted. The same amount was given intravenously to 2 subjects over 24 hours and proved to be only slightly anabolic. Intramuscular TP, on the other hand, proved to be definitely anabolic in smaller doses. The authors conclude that the anabolic effect of testosterone depends not on a high level acting for a short period but on a lower level persisting for a longer period of time. This was in contradistinction to a previous report from the same laboratory[36] where 150 to 200 mg. of testosterone in solution in human serum albumin given intravenously was found to cause significant nitrogen retention starting within the first 24 hours. In the same report, it was stated that 25 mg. of testosterone given intramuscularly daily caused a gradual fall in the excretion of nitrogen which reached in 4 to 8 days a positive balance equal in magnitude to that seen on the second day of the intravenous administration.

Creatine metabolism. Testosterone and MT have differential effects upon creatine excretion. In 4 patients with slight creatinuria, testosterone caused a decrease in excretion. After withdrawal of testosterone, there was a rebound with the peak value about three times the amount observed in the control periods. Keutmann, Bassett, and Kochakian[37] thought that the excess creatine excreted during the rebound exceeded what had been retained during androgen therapy. It was thought that testosterone possibly accelerated the synthesis of creatine and, when androgen therapy was discontinued, the effect on creatine synthesis rapidly ceased. MT and MAD administration was initially associated with a decrease in creatinuria for a few days followed by a gradual increase to levels far above those of the control periods. In the case of MAD, this continued for some time after withdrawal of therapy, and was followed by a decline. When MT was withdrawn, there was a marked rebound in the release of creatine which had previously been stored. Paradoxically, a steady increase of creatinine excretion was observed while both compounds were given, which would suggest that increased creatine had been deposited. The initial decrease in creatinuria caused by MT is in contrast to the usual

concept of increased creatinuria following MT administration.

In a study on the effect of TP and MT on the creatinuria of progressive muscular dystrophy,[38] it was found that TP administration caused no change in creatine output but, after withdrawal, marked creatinuria was seen for several days. MT administration, on the other hand, caused marked creatinuria but there was no increase after withdrawal of the medication. TP administration to normal subjects in this study caused a marked decrease in creatine excretion, with rebound after its withdrawal. MT administration to the normal controls caused increased creatinuria.

Testosterone analogues

Attempts have been made since the recognition of testosterone as an anabolic agent to improve the anabolic:androgenic ratio of the androgenic steroids in an effort to synthesize the ideal preparation the anabolic properties of which would be evident long before its virilizing potential was expressed. Unfortunately, none of the newer anabolic androgens are entirely free of virilizing effects if given in high enough doses. Nevertheless, as a result of the many attempts which have been made to modify the steroid nucleus, some new compounds have been synthesized, including the three steroids which will be discussed below. These are by far the most promising, although they still leave much to be desired as far as freedom from androgenic effects is concerned.

As has been discussed above, small, apparently insignificant changes in the steroid nucleus can cause significant alterations in the pharmacologic potential of the synthesized steroid. For example, it has been found that removal of the 19 carbon atom and/or unsaturation of the carbons 5-6 (rather than 4-5) results in less androgenic activity without impairing anabolism.

Norethandrolone (17-ENT) [NILEVAR®]

Norethandrolone, the 17-alpha methyl ester of 19-nortestosterone, was synthesized in an attempt to emphasize anabolic effects while diminishing androgenic properties. In comparison to TP, it has been found to have equivalent anabolic activity[1,39,40] but has approximately only one sixteenth the androgenic potential.[40,41] It has been said that "TP produces androgenic effects at a dose that is not anabolic whereas [17-ENT] is anabolic at a dose that is not androgenic."[1] It should be emphasized, however, that there is no question that 17-ENT can produce virilization including increased frequency of erection, enlargement of the clitoris, acne, hirsutism, and deepening of the voice. In one series, in which 1.5 mg. per kilogram was given daily for 10 days followed by 0.5 mg. per kilogram thereafter, there was evidence of some degree of virilization in 20 per cent of the patients.[42] For those who feel that 17-ENT is not androgenic at certain dose levels (usually about 1.2-1.5 mg. per kilogram), it should be emphasized that androgenicity might be demonstrable only with chronic and not with acute administration. For example, frequency of penile erection and increase in the size of the penis in young males are specific and sensitive measures of androgenicity. Such patients receiving doses of norethandrolone in excess of the amounts noted above will frequently show the stimulatory effects on the penis, provided the medication is continued for more than 1 month. In all instances of reported androgenicity, decreasing the dose or discontinuing the drug relieved most of the adverse symptoms noted except for occasional residual deepening of the voice. In the authors' experience, residual hirsutism has also been seen. Use of 20 mg. daily for 7 weeks in a small boy caused penile enlargement and pubic hair growth,[43] since the dose used exceeded 1 mg. per kilogram.

Decreased spermatogenesis has been noted in patients who have been treated with doses as low as 30 mg. daily, with a rebound seen after cessation of therapy.[42] This is not, however, a measure of the androgenicity of the compound but merely an

attribute of its potent gonadotrophin-inhibiting effect. Removal of the 19-methyl group enhances the gonadotrophin-inhibiting quality of many of the parent compounds so altered.

17-ENT also has significant progestational activity, but to a lesser degree than ethinyl nortestosterone. The endometrium does not appear to be as well supported by 17-ENT as it is by the other progestational agents of similar structure. Break-through bleeding occurred in a significant number of cases where 17-ENT was used as a progestational steroid.[42] This may be due, however, to lack of adequate concomitant estrogenic activity rather than inadequate progestational activity per se.

As far as mode of administration is concerned, 17-ENT is relatively well absorbed by oral administration and is five times as potent as MT and 19-nortestosterone in increasing levator ani muscle weight.[1] Intramuscular administration has been shown to be 1½[42] to 5[1] times as effective, on a milligram for milligram basis, as oral administration.

Experimental and metabolic aspects. Before discussion of the clinical uses of 17-ENT, it might be well to consider briefly some of the metabolic and experimental aspects of 17-ENT administration.

The effect of ENT on pituitary gonadotrophin was evaluated by Goldman and associates[44] with immature, castrated male rats joined in parabiosis to immature females. At doses of 10, 20, and 40 mcg. of 17-ENT daily, significant suppression of pituitary gonadotrophin occurred, although the higher doses gave a greater degree of suppression. These doses in parabiotic animals were anabolic without being significantly androgenic. The gonadotrophin-inhibitory effects were substantiated in the human in patients receiving 50 to 100 mg. of 17-ENT daily for 3 weeks or longer and who had normal or increased gonadotrophic hormone in the urine before therapy.[45] In these cases, the urinary gonadotrophic hormone fell to undetectable levels. In another report,[46] gonadotrophic hormone was inhibited in 2 patients with Klinefelter's syndrome and one menopausal woman by 20 and 40 mg. of 17-ENT per day, respectively. This is disputed by the data[43] on 4 patients with elevated resting levels in whom doses of 100 to 1,500 mg. daily produced little evidence of suppression, except possibly in one patient during the second week of therapy. However, there is no indication given in this paper of the duration of therapy.

17-ENT and MT have been found to be highly active in preventing the catabolism and soft tissue calcification that normally occur following intoxication with dihydrotachisterol in the rat.[47]

The effect of 17-ENT on the uptake of radioactive sulfur in intact and fractured humeri in normal and castrated male rats was studied by Kowalewski and Gouws.[48] The ratio of radioactivity of fractured:intact bone was calculated and it was found that castration resulted in a significant decrease in radioactivity of fractured specimen as compared to that in normal controls. However, 17-ENT given to castrated rats during the period of healing of the fracture stimulated the radioactive sulfur uptake in fractured bones, resulting in a ratio of radioactivity which was several times higher than the same ratio observed in untreated rats. This was carried further by the investigation of the effect of cortisone and 17-ENT on the radioactive sulfate uptake of young cockerels' leg bones. Cortisone was found to diminish, and 17-ENT to increase, the capacity of growing bones to bind labeled sulfate,[49] which is interpreted as a manifestation of the antianabolic and anabolic effects of these hormones, respectively. Comparable effects were also observed in the studies on the fractured rat humerus with radioactive sulfur uptake procedures. Cortisone was shown to impair significantly the repair of fractured humerus and 17-ENT was found to offset this effect when given simultaneously with cortisone or alone to rats pretreated with cortisone.[50]

The effect of 50 to 100 mg. of 17-ENT

daily in 4 males has been found to cause a decrease in the excretion of 17-ketosteroids and 17-ketogenic steroids.[51] In another study,[40] in which 11 female patients received 17-ENT, 25 mg. intramuscularly three times weekly for 10 weeks, 5 patients had decreased 17-ketosteroid excretions. Our experience is that 17-ketosteroids in females are not affected by 17-ENT. The depression of 17-ketosteroids in males on 17-ENT may be attributed to gonadotrophic hormone inhibition with resulting depressed endogenous testicular activity. Our data indicate that, in the doses used, 17-ENT does not inhibit adrenocortical secretion of the 17-ketosteroid precursors.

The effect of 17-ENT on creatine and creatinine excretion was studied by Dowben.[53] A mean increase of 393 mg. in daily excretion of creatine and an increase of 0.77 Gm. in daily excretion of total creatinine chromogen was observed in 6 patients after oral administration of 30 mg. 17-ENT daily for 6 weeks. The author feels that the alteration of creatine metabolism may possibly be part of the general anabolic effect of 17-ENT.

The effect of 17-ENT on blood lipids was studied by Meade and co-workers,[54] who administered 25 or 50 mg. of 17-ENT or a placebo to 57 chronically underweight individuals in a double blind study. On 50 mg. of 17-ENT daily, they found decreased alpha-lipoproteins, unchanged beta-lipoproteins, and decreased cholesterol and phospholipid levels equally in males and females, in both the young and older age groups. On 25 mg. of 17-ENT, moderate reductions in phospholipid and cholesterol levels were seen in both age groups with no change in lipoprotein in the younger patients and proportional changes in alpha and beta-lipoproteins in the older patients. Sachs and his associates[55] administered 25 to 75 mg. of 17-ENT daily intramuscularly to 10 patients for 30 to 35 days. They found a significant increase in serum alpha-2 and beta globulins in 9 of 10 subjects. In 8, there was an accompanying increase in beta-lipoproteins and, in 4 of these, an increase in the levels of chemically determined serum lipids was also noted. These effects were found to be evident as early as 3 days after the beginning of the administration of the steroid. There was no breakdown of these patients according to age groups.

Clinical application

Many observations on the clinical use of 17-ENT may be found in the literature. The following are only representative of the main therapeutic areas in which 17-ENT has been found to be efficacious.

Since, despite its obvious disadvantages, testosterone found wide application in the therapy of healthy underweight as well as debilitated individuals, it was natural that hopes were high when 17-ENT made its appearance, especially since it was felt at first that this preparation truly divorced its anabolic effects from its androgenic potential. In a 6 month, double blind evaluation[56] of the drug in 54 underweight subjects (including patients with chronic diseases), the mean weight increase of the patients on either 25 or 50 mg. daily was 9 pounds. These data are in contrast to the results obtained with patients on placebo therapy, in whom no significant weight increase was obtained under similar experimental conditions. After cessation of therapy, 25 subjects were observed for another 6 months and 19 of these either maintained their weight or continued to gain.

In a British study,[57] 4 elderly underweight males showed a significant weight increase associated with nitrogen retention while on 17-ENT. The total and extracellular body water was measured and the results supported the fact that weight increase was not due to fluid retention but to an increase in lean body mass.

In a study of 38 patients[46] ranging in age from 2 to 58 years, both underweight normal subjects and patients with gonadal or pituitary failure, a dose level of 0.5 mg. per kilogram caused frequent androgenicity in the hypogonadal or prepubertal male. On 20 to 30 mg. per day, over an

average of 8.6 weeks, 29 gained an average of 5.39 pounds, 8 lost an average of 3.73 pounds, and one showed no weight change. Parenthetically, because of its progestational activity, the drug produced menstrual irregularities in underweight females with regular menses.

Spencer and collaborators[58] evaluated the effects of a daily 50 mg. intramuscular dose of 17-ENT. They noted a significant decrease in urinary nitrogen, phosphorus, and potassium excretion as well as a positive metabolic balance of these constituents with an accompanying gain in weight. There was no significant retention of salt or water and the anabolic effect lasted for a few days after cessation of therapy.

The use of 17-ENT in underweight children has resulted frequently in weight increases.[42,59] The effect on skeletal maturation has been of some concern as it was in the case of testosterone. In Bayer's study,[59] 4 boys ranging in age from 12 years to 16 years, 3 months, and one girl, 13 years, 11 months, were studied. All were short and all but one boy were retarded in skeletal and sexual maturation. The patients were given 10 mg. of 17-ENT daily for 6 months. The results indicated that the secondary sexual characteristics had matured in all but the youngest boy. There was no disproportion of sexual characteristics and no masculinization of the female. It was found that the skeletal maturation had kept pace with the anticipated changes due to age alone while the girl's skeletal age had advanced more than that expected merely from maturation alone. In another study, 6 children with retarded growth were given a dose of 0.5 mg. per kilogram daily for a period of 6 months. An average height increase of 5.1 cm. was noted in the girls and 5.2 cm. in the boys, whereas previous 6 month measurements had shown only 1.9 cm. and 1.8 cm. increases, respectively. In further studies[42] in these children, no evidence of acceleration of skeletal maturation was seen after 13 months. Comparable effects have been noted by our group[61]; the administration of different doses of 17-ENT caused significant increases in height, without any significant effect upon acceleration of skeletal maturation of children with diminished stature including two patients with gonadal dysgenesis.

In summary, although the available literature would suggest that acceleration of skeletal maturation is an infrequent side effect of 17-ENT therapy, further long-term studies are necessary to support these preliminary impressions. At present, the evidence appears to be in favor of the fact that despite its growth-enhancing effect epiphyseal closure is uncommon with 17-ENT when modest doses are employed.

The anabolic 19-norsteroids have been used in the treatment of acute and chronic renal failure. The rationale for their use in such patients is based on the concept that the anabolic steroids would diminish the catabolic breakdown of tissue, therefore requiring less work of the kidney for the elimination of such end products. In addition, it was felt that this steroid would have some renotrophic effect similar to that reported with testosterone.[9] In 10 cases of severe chronic renal failure,[62] there was an increase in appetite, gain in body weight, and improvement in the clinical condition on 50 to 100 mg. of 17-ENT daily by mouth or on nandrolone phenpropionate, 50 mg. intramuscularly per week. During treatment, not only was there no increase in urea nitrogen but, at times, there appeared to be a profound decrease. No specific laboratory data are given. Six of 15 patients in the acute renal failure group[63] were obstetric patients. In these, there was a distinct suppression of urea production with relatively little effect in the nonobstetric group or in the controls on low-protein diets.

17-ENT has been used in the postgastrectomy state[64] where it was found that, in 10 of 13 cases, administration caused a weight increase of from 2 to 11 pounds. This is not uniformly true in all cases, however, and "it would appear . . . that 17-ENT can induce a weight gain in patients with nutritional problems following partial

gastrectomy in a majority of instances but exceptions are noted even when malabsorption is absent."[42] The use of 17-ENT in daily intramuscular doses of 25 and 50 mg. in patients subjected to major pelvic surgery was followed by a positive nitrogen balance as compared to a consistently negative balance in patients on placebo.[65] The authors stated that similar results were achieved with 17-ENT in patients with major fractures. Reversal of otherwise negative nitrogen balance accompanied administration of the steroid.

17-ENT has been employed in 2 patients with Fanconi's syndrome who were given 10 to 20 mg. a day for 8½ months. Sustained gains in height and weight were noticed as well as a decrease in the cystinuria to normal values.[66] Clinically, these patients showed temporary but definite signs of increased strength and interest in their surroundings. This was in contrast to their previous lethargic state.

The evidence for the effect of 17-ENT on calcium retention is conflicting. There are reports[42] of amelioration of pain, increased sense of well being and weight gain in patients with osteoporosis without evidence of significant x-ray changes. However, these effects may be due to the anabolic activity of the drug and not to specific metabolic activity or anabolic effects that could be accomplished without obvious changes in x-ray findings.

17-ENT has been found to cause disturbance of liver function in a significant number of cases. In one study,[67] abnormal BSP retention was found in 74 per cent of 47 patients who had received 17-ENT for underweight. Other liver function studies were normal in all but 2 of these cases, which showed slight but reversible increase in bilirubin and alkaline phosphatase. A short-term study in 10 patients indicated that 25 mg. daily of 17-ENT would result in BSP and SGOT abnormalities within 2 to 3 weeks while a 50 mg. dose per day resulted in comparable abnormalities after only one week of therapy. The authors postulate that 17-ENT inhibits the transfer of BSP into bile. Although BSP retention appears to be by far the most common hepatic abnormality associated with 17-ENT administration (with no evident clinical manifestations), jaundice has also been reported.[68,69] This is probably due to cholestasis[68] and is associated with some elevation of alkaline phosphatase as well as the presence of bile and urobilinogen in the urine. Interestingly enough, 17-ENT has brought about an elevation of SGOT in patients with (as well as without) jaundice.[68]

Nandrolone phenpropionate (NPP)

This is the phenyl propionate ester of 19-nortestosterone, the ester replacing the beta-OH group at the 17 C atom. The beta substitution is said to have an advantage over the alpha substitution as far as liver complications are concerned in the sense that both 17-ENT and MT can cause jaundice.[70] NPP has been reported to cause questionable BSP retention in only one case.[70] However, one must admit that control studies with this agent, in adequate doses, are still lacking.

Experimental aspects. A daily dose of 200 mg. given for 7 days to 50 gram castrated male rats induced active stimulation of the levator ani muscle and relatively little activity as far as seminal vesicle weight was concerned. There was some associated atrophy of the adrenals and thymus. NPP appears to have a hysterotrophic effect, which is apparently direct since it also occurs in castrated animals. This parenteral steroid will also induce some atrophy of the ovaries of the rat, probably by virtue of the gonadotrophic hormone inhibiting effect of the steroid. NPP also has a renotrophic effect which is less pronounced than that of testosterone. NPP nullifies, to a certain extent, the weight loss noted in hydrocortisone-treated rats.[71] In the therapy of young male rats with cortisone, adrenal atrophy was observed as well as marked weight loss. When comparable doses of cortisone were used in conjunction with NPP, less adrenal atrophy and body weight loss were noted.[72]

Clinical applications. NPP appears to be as potent an anabolic agent as 17-ENT but has the advantage of being longer acting in that one injection of 25 to 50 mg. per week results in demonstrable effects during this period of time. In one study, the effects of parenteral NPP were found to last for 15 days.[71] In 48 cases of postmenopausal women on a routine diet, a weekly 50 mg. injection of NPP caused a significant weight increase in the treated groups while no weight increase was noted in the control groups. The largest weight increase was reported in the patients undergoing therapy for the longest period of time (12 weeks).[70] In the same study, 25 mg. of NPP given intramuscularly every 5 days (which is more frequent than is usually recommended) caused menstrual irregularities and amenorrhea. This no doubt was due to gonadotrophic hormone inhibition by the steroid. There are no data to support this hypothesis, however. For an undisclosed number of times per week, 5 mg. of NPP caused a weight gain in underweight children, but the response achieved appeared to be somewhat inferior to that noted with 25 mg. of testosterone.[73]

The virilizing effects of NPP appear to be slight,[73] but doses in excess of 100 mg. weekly have caused increased frequency of erection, lengthening of the penis, and enlargement of the clitoris.[74] This is in agreement with the usual experience with the norsteroids in that, if doses are high enough, virilization would be expected.

NPP evidently may cause fluid retention, doses of 25 mg. every 3 days having caused edema.[75] In contrast, Johnson[70] states, as a result of body water studies, that, if anything, 50 mg. of NPP per week causes a decrease in body water.

In the treatment of osteoporosis, NPP appears to have the same effect as the other 19 norsteroids—that is, palliation with variable effects on calcium excretion. Nowakowski and Parada[76] found calcium and nitrogen retention in patients treated with NPP for the osteoporosis of Cushing's syndrome. No significant retention was found in idiopathic osteoporosis despite striking clinical improvement. In a study on the effect of NPP on osteoporosis, 25 mg. of the steroid was given every one to 2 weeks to 18 patients. On this regime, 10 patients had complete relief from pain and 6 had approximately 75 per cent improvement.[75] No calcium balance studies were included in this paper. In patients with metastases to bone from breast carcinoma,[77] it was found that administration of NPP resulted in a marked decrease in calcium excretion with a positive nitrogen balance.

NPP, like 17-ENT, in doses of 50 mg. weekly, was found to decrease the levels of nitrogenous waste products of the serum in patients with uremia as well as to increase body weight.[62]

In our experience with 2 hypogonadal male patients on 50 mg. of NPP 3 times weekly, we noted a decrease in 17-ketosteroid excretion without alteration in the 17-hydroxycorticoid levels, while the gonadotrophic hormone titer was diminished.

Methylandrostenediol (MAD)

Experimental. The response of the patient or animal to MAD is dependent upon the route of administration which is employed. Orally, in animal experiments, it has been found to exhibit some androgenic activity as well as a capacity to inhibit the growth of certain experimental tumors.[78] Its anabolic effect, however, has been found to be more marked by parenteral than by oral administration. A review of the data[78] suggests that oral MAD is 0.4 to 1.0 times as active as oral MT as an androgen; parenteral administration reveals a much less marked androgenic effect, MAD being 0.02 (in the capon) and 0.3 (in the rat) times as active as testosterone.

Spermatogenesis has been maintained in hypophysectomized rats with a dose of 2 mg. of MAD per day.[78]

As far as the anabolic effect is concerned, balance studies in castrate dogs on average intramuscular doses of 6 mg. daily have shown nitrogen retention. Daily oral

doses of 200 mg. did not lead to nitrogen retention.[78]

By use of the levator ani assay technique, MAD was found to be a potent myotrophic agent in a dose of 1 mg. per kilogram given subcutaneously. In this study, androgenic properties were found only at the very high doses of 50 mg. per kilogram.[79,80]

Male and female rats, 3½ months old, on 0.3 to 0.5 mg. of MAD, administered daily by subcutaneous injection for 20 to 28 days, showed distinct and definite weight gains. After the cessation of therapy, chemical analysis of the whole rat showed a gain of protein and water and a loss of fat as a result of MAD administration. These changes are interpreted by the authors as evidence for tissue growth.[81] On the other hand, levator ani assays done by Hershberger[82] suggested that MAD had only 5 per cent of the anabolic potency of TP with no separation of anabolic and androgenic activities. Also working with castrated rats, Saunders and Drill[39] found that, when compared to TP, MAD was only 5 per cent as potent in increasing the levator ani weight by 50 per cent. The anabolic:androgenic ratio was found to be only 1.58 (that of TP being 1), suggesting relatively little separation in anabolic:androgenic effects.

MAD can produce a syndrome of nephrosclerosis, periarteritis, and myocarditis in unilaterally nephrectomized rats maintained on high-salt intake.[83] To the reviewers' knowledge, no clinical counterparts of these experiments have been reported.

Prevention of adrenal atrophy caused by cortisone administration has been reported with the use of MAD.[84] Yet there was no evidence that MAD could alter the response of the patient with the adrenogenital syndrome to cortisone.[84A]

Parenteral MAD has been reported to have a renotrophic effect in mice.[78]

Clinical data. MAD has been estimated to have approximately one-fifth the protein anabolic activity of testosterone.[78] In one series of hospitalized patients,[85] who received a total of from 26 to 80 Gm. MAD orally and/or parenterally, there was retention of nitrogen and the protein catabolic effect of ACTH was counteracted. There was no notable effect of MAD on serum calcium and phosphorus in 4 patients with carcinoma of the breast. However, an additional patient developed hypercalcemia, an occurrence which might well have been caused by the natural history of the disease. Except for moderate hirsutism there was no evidence of virilization.

McSwiney and Prunty[86] found that oral doses of 50 and 200 mg. of MAD per day produced no consistent effects. However, 400 mg. per day by mouth or 200 mg. per day intramuscularly caused nitrogen retention. Compared to the significant nitrogen retention caused by 25 mg. of TP and MT per day, equivalent doses of MAD were found to induce a much smaller measure of nitrogen retention. The level of retention, however, is so small that these data may well be within the range of error (76 mg. per kilogram per day compared to less than 26 mg. per kilogram per day).[22]

MAD has been used in underdeveloped children.[87] In 15 patients aged 2 months to 7 years, 1.5 to 3 mg. of MAD per kilogram of body weight was given intramuscularly two to three times weekly with 5 to 6 mg. per kilogram given on three occasions. In all cases, after several injections, increases in height and weight were noted. These changes exceeded what was expected from normal children of this age. At times, differences between control and treated groups were minimal. Weight increases virtually ceased when therapy was stopped, but recurred when MAD was resumed. No data on skeletal maturation were given. If doses were increased to 5 mg. per kilogram or medication was given more frequently than twice weekly, undesirable side effects, such as sterile abscesses and enlargement of the clitoris as well as growth of pubic hair, were noted. Doses of 1.5 mg. per kilogram twice weekly were found to be safe and effective means of treatment, however.

Infants have been treated with MAD with a resultant decrease in blood amino acids. This is thought to be due to the protein anabolic effect of the steroid.[88]

Creatinuria, as in MT therapy, has been found to be very marked on MAD,[78] but no data on creatinuria after cessation of therapy are given.

Thirty-three patients with osteoporosis were treated with a daily buccal dose of 25 mg. of MAD. They were observed for an average of 18 months. Satisfactory relief of pain was observed in 27 patients and a poor response was seen in 6 patients. No calcium balance studies were reported.[89] These data are in agreement with the experiences previously described in the use of testosterone and the 19-norsteroids in osteoporosis.

In a study on a young man on 100 mg. of cortisone daily for severe ankylosing spondylitis, administration of 100 mg. of MAD daily resulted in decreased urinary and fecal calcium and in a positive calcium balance.[90]

It is definitely known that the androgenic steroids are beneficial in the therapy of osteoporosis. Correlation between calcium metabolism and clinical improvement in patients treated with the norsteroids and MAD requires further investigation. The effect of testosterone on calcium metabolism has already been discussed.

Estrogen

Experimental aspects. Including estrogen among the anabolic drugs is warranted on the basis of its highly potent selective growth stimulus for the breasts, uterus, and lower femal genital tract. Estrogen is also well known as a potent inhibitor of pituitary gonadotrophin. Indeed, in high doses, it may inhibit all modalities of pituitary function. The latter was demonstrated by Zondek[91] in the cock, where doses up to 25,000 I.U. of estradiolbenzoate twice weekly inhibited only gonadotrophic function, while larger doses of 50,000 I.U. twice weekly not only inhibited gonadotrophic secretion but also induced a distinct retardation of growth which became accentuated as treatment progressed. This differential sensitivity of the pituitary to large doses of estrogen has also been demonstrated in the rat.[91]

Castration in animals may lead to apparently paradoxical weight increase. This, however, is not due to protein anabolism but merely to fat deposition.

The anabolic effects of estrogen on the protein matrix of skin and bone are less well known and merit brief discussion. Goldzieher and associates[11] performed serial studies on the effects of topical steroids on the skin of 27 elderly patients. They found that administration of estrogen caused proliferation of the epidermis, progressive development of the rete pegs and papillae, and an increase in the proliferation of keratohyalin granules, as well as new formation of elastic fibrils and increased vascularization of the cutis. Interestingly enough, high doses did not increase this effect and prolonged administration led, in some cases, to skin atrophy.

Reifenstein and Albright[92] have demonstrated that urinary nitrogen excretion undergoes a poorly sustained decrease during estrogen therapy. Eleven cases of osteoporosis, including 3 secondary to Cushing's syndrome, were treated with estrogens. Decreased calcium and phosphorus excretion was noted and it was further observed that the above effect on calcium metabolism was greater with a combination of estrogens and androgens than with either one alone in postmenopausal and senile osteoporosis. Henneman and Wallach[93] found that estrogen therapy caused significant calcium retention in the female; the same occurred with MT in the male. In their series of 200 postmenopausal women treated for osteoporosis for 1 to 20 years with estrogen, the process of the osteoporosis was arrested in nearly all instances. In postmenopausal osteoporosis, Perloff and co-workers[94] have found that relief of bone pain and reversal of negative calcium balance may be achieved within 4 to 6 weeks by 1.5 mg. of piperazine estrone sulfate and 5 mg. of MT daily. The effect of with-

drawal of estrogen on 2 oophorectomized subjects and of oophorectomy on one subject was investigated. A slight increase in nitrogen excretion was noted as well as accentuation of the negative calcium balance.[95] Estrogen has also been found useful in the therapy of Paget's disease and in the prevention of vertebral fractures secondary to corticosteroid administration.[96]

The balance studies of Whedon and Shorr[97] show that alpha estradiol benzoate in the dose of 10,000 to 20,000 units daily actually caused an average daily nitrogen loss of 0.78 Gm. in patients convalescing from paralytic poliomyelitis. The pattern of creatinuria and increase in urinary glycocyamine while the patients were on this estrogen suggested that this steroid causes an increase in the synthesis of creatine but not in its storage. This is in contrast to TP, which probably does both. In the estrogen study,[97] a slight but definite increase in urinarly calcium was noted, a fact which is at variance with the results of other balance studies.[92,93,95]

References

1. Drill, V. A., and Saunders, F. J.: Androgenic and Anabolic Action of Testosterone Derivatives. Hormones and the Aging Process, New York, 1956, Academic Press, Inc., pp. 99-113.
2. Organon Inc.: Questions and Answers on Durabolin.
3. Kochakian, C. D., and Murlin, J. R.: The Effect of Male Hormone on the Protein and Energy Metabolism of Castrate Dogs, J. Nutrition **10**:437-457, 1935.
4. Papanicolaou, G., and Falk, E. A.: General Muscular Hypertrophy Induced by Androgenic Hormone, Science **87**:238-239, 1938.
5. Nimni, M. E., and Geiger, E.: Non-suitability of Levator Ani Method as an Index of Anabolic Effect of Steroids, Proc. Soc. Exper. Biol. & Med. **94**:606-610, 1957.
6. Eisenberg, E., and Gordan, G. S.: The Levator Ani Muscle of the Rat as an Index of Myotrophic Activity of Steroidal Hormones, J. Pharmacol. & Exper. Therap. **99**:38-44, 1950.
7. Gordan, G. S.: Experimental Basis for Anabolic Therapy, A.M.A. Arch. Int. Med. **100**:744-749, 1957.
8. Kinsell, L. W., Reifenstein, E. C., Jr., Bryant, D., and Albright, F.: The Quantitation of Axillary Hair Growth as an Index of Endocrine Function, J. Clin. Endocrinol. **6**:463-464, 1946.
9. Selye, H.: The Effect of Testosterone on the Kidney, J. Urol. **42**:637-641, 1939.
10. Greenblatt, R. B., and Kupperman, H. S.: Further Studies on the Control of Menorrhagia, J. Clin. Endocrinol. **6**:675-687, 1946.
11. Goldzieher, J. W., Roberts, I. S., Rawls, W. B., and Goldzieher, M. A.: Local Action of Steroids on Senile Human Skin, A.M.A. Arch. Dermat. & Syph. **66**:304-315, 1952.
12. Kochakian, C. D., and Dolphin, J.: The Protein-Anabolic Effect of Testosterone Propionate in the Hypothyroid Rat, Am. J. Physiol. **180**:317-320, 1955.
13. Kochakian, C. D., and Webster, J. A.: Effect of Testosterone Propionate on the Appetite, Body Weight and Composition of the Normal Rat, Endocrinology **63**:737-742, 1958.
14. Kochakian, C. D.: Comparison of Protein Anabolic Property of Various Androgens in the Castrated Rat, Am. J. Physiol. **160**:53-61, 1950.
15. Kochakian, C. D., Moe, J. G., and Dolphin, J.: Protein Anabolic Effect of TP in Adrenalectomized and Normal Rats, Am. J. Physiol. **162**:581-589, 1950.
16. Kochakian, C. D., Robertson, E., and Bartlett, M. N.: Sites and Nature of Protein Anabolism Stimulated by Testosterone Propionate in the Rat, Am. J. Physiol. **163**:332-346, 1950.
17. Meyer, R. K., and Hershberger, L. G.: Effects of Testosterone Administration on Acid Soluble and Insoluble Glycogen in the Levator Ani Muscle, Endocrinology **60**:397-402, 1957.
18. Wijnans, M., and DeGroot, C. A.: Contribution to the Knowledge of the Protein Anabolic Effect of Testosterone Propionate, Acta physiol. et pharmacol. neerl. **3**:85-94, 1953.
19. Perlman, P. L., and Cassidy, J. W.: Influence of Nitrogen Intake on Nitrogen-Retaining Action of Testosterone Propionate, Proc. Soc. Exper. Biol. & Med. **83**:674-675, 1953.
20. Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F. C.: The Effect of Testosterone Propionate on Nitrogen, Electrolyte, Water, and Energy Metabolism in Eunuchoidism, Endocrinology **23**:135-153, 1938.
21. Kenyon, A. T., Knowlton, K., and Sandiford, I.: The Anabolic Effects of the Androgens and Somatic Growth in Man, Ann. Int. Med. **20**:632-654, 1944.
22. Wilkins, L., and Fleischmann, W.: The Influence of Various Androgenic Steroids on Nitrogen Balance and Growth, J. Clin. Endocrinol. **6**:382-401, 1946.
23. Shelton, E. K., and Varden, A. E.: The Use of Methyl Testosterone in the Treatment of Premature Infants, J. Clin. Endocrinol. **6**:812-816, 1946.

24. Hellinga, G.: Growth Promoting Treatment in Small Children, Acta endocrinol. **18**:536,-547, 1955.
25. Sobel, E. H., Raymond, C. S., Quinn, K. V., and Talbot, N. B.: The Use of Methyltestosterone to Stimulate Growth: Relative Influence on Skeletal Maturation and Linear Growth, J. Clin. Endocrinol. **16**:241-248, 1956.
26. Van Wayjen, R. G. A., Groen, J., and Willebrands, A. F.: Application of the Protein-Saving Effect of Androgenic Hormones in the Treatment of Patients Following Total Gastroectomy, Gastroenterology **36**:599-612, 1959.
27. Cooper, I. S., Rynearson, E. H., MacCarty, C. S., and Power, M. H.: Testosterone Propionate As a Nitrogen-Sparing Agent After Spinal Cord Injury, J. A. M. A. **145**:549-553, 1951.
28. Albright, F., Parson, W., and Bloomberg, E.: Therapy in Cushing's Syndrome, J. Clin. Endocrinol. **1**:375-384, 1941.
29. Talbot, N. B., Butler, A. M., and MacLachlan, E. A.: The Effect of Testosterone and Allied Compounds on the Mineral, Nitrogen, and Carbohydrate Metabolism of a Girl With Addison's Disease, J. Clin. Invest. **22**:583-593, 1943.
30. Crispell, K. R., Williams, G. A., Parson, W., and Hollifield, G.: Metabolic Studies in Myxedema Following Administration of L-triiodothyronine. 1) Duration of Negative Nitrogen Balance; 2) Effect of Testosterone Propionate; 3) Comparison With Nitrogen Balance in a healthy volunteer, J. Clin. Endocrinol. **17**:221-231, 1957.
31. Foss, G. L.: Clinical Administration of Androgens, Lancet **1**:502-504, 1939.
32. Emmens, C. W., and Parkes, A. S.: The Effect of Route of Administration on the Multiple Activities of Testosterone and Methyl Testosterone in Different Species, J. Endocrinol **1**:323-331, 1939.
33. Kupperman, H. S., Aronson, S. G., Gagliani, J., Parsonnet, M., Roberts, M., Silver, B., and Postiglione, R.: The Value of Various Laboratory Procedures in the Comparative Study of the Duration of Action of Androgens, Acta Endocrinol. **16**:101-117, 1954.
34. Sakamoto, W., Gordan, G. S., and Eisenberg, E.: Prolongation and Potenetiation of Anabolic and Androgenic Effects of Steroids: Testosterone and Methylandrostenediol, Proc. Soc. Exper. Biol. & Med. **76**:406-408, 1951.
35. Brown, H., and Samuels, L. T.: Effect of Intravenous Testosterone on Nitrogen Balance in Man, J. Clin. Endocrinol. **16**:775-778, 1956.
36. West, C. D., Tyler, F. H., and Brown, H.: The Effect of Intravenous Testosterone on Nitrogen and Electrolyte Metabolism, J. Clin. Endocrinol. **11**:833-841, 1951.
37. Keutmann, E. H., Bassett, S. H., and Kochakian, C. D.: The Influence of Testosterone Propionate, Methyl Testosterone and Methyl Androstenediol on Creatine Metabolism, Endocrinology **35**:222-223, 1944.
38. Hoagland, C. L., Shank, R. E., and Gilder, H.: Effect of Testosterone Propionate and Methyl Testosterone on Creatinuria in Progressive Muscular Dystrophy, Proc. Soc. Exper. Biol. & Med. **55**:49-51, 1944.
39. Saunders, F. J., and Drill, V. A.: Comparative Androgenic and Anabolic Effects of Several Steroids, Proc. Soc. Exper. Biol. & Med. **94**:646-649, 1957.
40. Goldfarb, A. F., Napp, E. E., Stone, M. L., Zuckerman, M. B., and Simon, J.: The Anabolic Effects of Norethandrolone, a 19-Nortestosterone Derivative, Obst. & Gynec. **11**:454-458, 1958.
41. Drill, V. A., and Saunders, F. J.: Biologic Effects of Nilevar, in Proceedings of a Conference on the Clinical Use of Anabolic Agents, April 9, 1956, pp. 4-5.
42. G. D. Searle and Company: Clinical Review of Nilevar.
43. Prunty, F. T. G., Brooks, R. V., Clayton, B. E., and McSwiney, R. R.: Some Effects of 17α-Ethyl-19-Nortestosterone in Man, Proc. Roy. Soc. Med. **51**:21-22 (Sec. Endocr.), 1958.
44. Goldman, J. N., Epstein, J. A., and Kupperman, H. S.: A Comparison of the Pituitary Inhibiting, Anabolic and Androgenic Effects of Norethandrolone in the Parabiotic Rat, Endocrinology **61**:166-172, 1957.
45. Leach, R. B., Paulsen, C. A., Lanman, J., Goldston, N. W., and Maddock, W. O.: Norethandrolone: Gonadotrophin Suppression Without Androgenic or Estrogenic Activity, Clin. Res. **6**:261-262, 1958.
46. Epstein, J. A., Vosburgh, L., Reid, G., and Kupperman, H. S.: Clinical Studies on Norethandrolone: an Anabolic, Progestational Agent, Clin. Res. Proc. **5**:16, 1957.
47. Selye, H., and Renaud, S.: On the Anticatabolic and Anticalcinotic Effects of 17-Ethyl-19-Nortestosterone, Am. J. M. Sc. **235**:1-6, 1958.
48. Kowalewski, K., and Gouws, F.: The Effect of 17-Ethyl 19-Nortestosterone (Nilevar) on the Uptake of Radiosulfur in the Fractured Humerus in the Rat, Surg. Gynec. & Obst. **105**:1-4, 1957.
49. Kowalewski, K.: Uptake of Radiosulfate in Growing Bones of Cockerels Treated With Cortisone and Certain Anabolic-Androgenic Steroids, Endocrinology **63**:759-764, 1958.
50. Kowalewski, K., and Gort, J.: An Anabolic Androgen as a Stimulant of Bone Healing in Rats Treated With Cortisone, Acta endocrinol. **30**:273-276, 1959.
51. Brooks, R. V., and Prunty, F. T. G.: The Sup-

pression of Adrenocortical Secretion With 17-Ethyl-19-Nortestosterone, J. Endocrinol. **15**:385-392, 1957.

52. Carter, A. C., Weisenfeld, J., and Goldner, M. G.: Failure of 17α-Ethyl-19-Nortestosterone to Effect Plasma 17-Hydroxycorticosteroids and ACTH Responsiveness in Man, Proc. Soc. Exper. Biol. & Med. **98**:593-594, 1958.
53. Dowben, R. M.: Increased Creatine and Creatinine Excretion After 17α-Ethyl-19-Nortestosterone, Proc. Soc. Exper. Biol. & Med. **98**:644-645, 1958.
54. Meade, R. C., Owenby, J., and Kory, R. C.: The Effect of Long-Term Administration of an Anabolic Drug, Norethandrolone, on the Blood Lipids of Chronically Underweight Individuals, J. Lab. & Clin. Med. **50**:932, 1957.
55. Sachs, B. A., Danielson, E., and Weston, R. E.: Effects of the Synthetic Anabolic Steroid, 17-Ethyl-19-Nortestosterone on Serum Proteins, Lipoproteins and Lipids in Human Subjects, J. Clin. Endocrinol. **16**:1388-1391, 1956.
56. Watson, R. N., Bradley, M. H., Callahan, R., Peters, B. J., and Kory, R. C.: A Six Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons. I. Weight Gain, Am. J. Med. **26**:238-243, 1959.
57. Woodford-Williams, E., and Webster, D.: An Anabolic Study With Norethandrolone in Four Elderly Underweight Males, Brit. M. J. **2**:1447-1450, 1958.
58. Spencer, H., Berger, E., Charles, M. L., Gottesman, E. L., and Laszlo, D.: Metabolic Effects of 17-Ethyl-19-Nortestosterone in Man, J. Clin. Endocrinol. **17**:975-984, 1957.
59. Bayer, L. M.: Growth Observations During the Administration of a New Steroid, Stanford M. Bull. **15**:308-315, 1957.
60. Whitelaw, M. J.: The Effects of 17-Ethyl-19-Nortestosterone (Nilevar) on Growth in Prepubertal Boys and Girls, Proc. 40th Meeting, The Endocrine Society, June, 1958, Article No. 163, p. 106.
61. Kupperman, H. S.: Unpublished data.
62. Gjorup, S., and Thaysen, J.: Anabolic Steroids in Treatment of Uremia, Lancet **2**:886-887, 1958.
63. McCracken, B. H., and Parsons, F. M.: Use of Nilevar to Suppress Protein Catabolism in Acute Renal Failure, Lancet **2**:885-886, 1958.
64. Lichstein, J.: Norethandrolone in the Postgastrectomy State: Effect on Weight Loss, Am. J. Gastroenterol. **31**:662-672, 1959.
65. Peden, J. C., Jr., Maxwell, M. C., and Ohin, A.: Anabolic Effect of a New Synthetic steroid on Nitrogen Metabolism After Operation, A.M.A. Arch. Surg. **75**:625-630, 1957.
66. Kupperman, H. S.: Unpublished data.
67. Kory, R. C., Bradley, M. H., Watson, R. N., Callahan, R., and Peters, B. J.: A Six Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons. II. BSP Retention and Liver Function, Am. J. Med. **26**:243-248, 1959.
68. Schaffner, F., Popper, H., and Chesrow, E.: Cholestasis Produced by the Administration of Norethandrolone, Am. J. Med. **76**:249-254, 1959.
69. Dunning, M. F.: Jaundice Associated with Norethandrolone (Nilevar) Administration, J. A. M. A. **167**:1242-1243, 1958.
70. Johnson, P.: A New Tissue Building Agent, Durabolin Symposium, Oct. 14, 1959.
71. Overbeek, G. A., and deVissen, J.: Nor-Androstenolone-Phenylpropionate. A New Potent Anabolic Ester, Acta Endocrinol. **24**:209-219, 1957.
72. Rinne, U. K., and Naatanen, E. K.: The Effect of Nor-Androstenolone Phenylpropionate on the Atrophy of the Adrenal Cortex and Inhibition of Growth Induced by Cortisone Acetate, Acta endocrinol. **27**:423-431, 1958.
73. Jonxis, J. H., and Maats, B. C.: The Influence of Durabolin on the Weight Increase of Children, Nederl. tijdschr. geneesk. **101**:389-392, 1957.
74. Ungari, C., and Rossoni, C.: The Use of a New Anabolic Steroid With Prolonged Action in Pediatrics, Aggiorn. Pediat. **9**:311-338, 1958.
75. Banghart, H. E.: Some Observations on Osteoporosis, Bull. Acad. Med. New Jersey, **5**:70-76, 1959.
76. Nowakowski, H., and Parada, J.: Klinische Erfahrungen mit 19-Nortestosteron phenylpropionate, Deutsche med. Wchnchr. **83**:1421-1426, 1958.
77. Werff, J. T. van der: Sex Hormones and Mammary Cancer: Experience With Durabolin, Brit. M. J. **2**:881-883, 1958.
78. Henderson, E., and Weinberg, M.: Methylandrostenediol, J. Clin. Endocrinol. **11**:641-652, 1951.
79. Gordan, G. S., Eisenberg, E., and Moon, H. D.: A Steroid Which Promotes Tissue Growth Without Concomitant Genital Activity, J. Clin. Endocrinol. **10**:807, 1950.
80. Gordan, G. S., Eisenberg, E., Moon, H. D., and Sakamoto, W.: Methylandrostenediol: A Protein Anabolic Steroid With Little Androgenic Activity, J. Clin. Endocrinol. **11**:209-212, 1951.
81. Korner, A., and Young, F. G.: The Influence of Methylandrostenediol on the Body Weight and Carcass Composition of the Rat, J. Endocrinol. **13**:78-83, 1955.
82. Hershberger, L. G., Shipley, E. G., and Meyer, R. K.: Myotrophic Activity of 19-Nortestosterone and Other Steroids Determined by

Modified Levator Ani Muscle Method, Proc. Soc. Exper. Biol. & Med. **83**:175-180, 1953.

83. Salgado, E., and Selye, H.: The Production of Hypertension, Nephrosclerosis and Cardiac Lesions by MAD Treatment in the Rat, Endocrinology **55**:550-560, 1954.
84. Winter, C. A., Hollings, H. L., and Stebbins, R. B.: The Effect of Androgenic Hormones Upon the Adrenal Atrophy Produced by Cortisone Injections, and Upon the Anti-inflammatory Action of Cortisone, Endocrinology, **52**:123-134, 1953.

84A. Kupperman, H. S., Finkler, R., and Burger, J.: Failure of Methylandrostenediol to Inhibit Adrenal Suppression by Cortisone in the Human, J. Clin. Endocrinol. **14**:810-811, 1954.

85. Homburger, F., Dart, R. M., Bonner, C. D., Branche, G., Jr., Kasdon, S. C., and Fishman, W. H.: Some Metabolic and Biochemical Effects of Methyl Androstenediol, J. Clin. Endocrinol. **13**:704-711, 1953.
86. McSwiney, R. R., and Prunty, F. T. G.: Metabolic Effects of Three Testosterone Derivatives Including 17-Ethyl 19-Nortestosterone, J. Endocrinol. **16**:28-40, 1957.
87. Awwaad, S.: Clinical Studies on the Effect of Methylandrostenediol Therapy in Infancy and Childhood, A.M.A. Arch. Pediat. **71**:285-290, 1954.
88. Caffarena, G., and Chiossi, A.: In Giordano, G., and Masciocco, D.: Studies on Methylandrostendiol. I. Bibliographic Review. Arch. Maragliano pat. clin. **10**:93-104, 1955.
89. Banghart, H. E.: A Clinical Evaluation of Methylandrostenediol in the Treatment of Osteoporosis, Am. Pract. & Digest Treat. **5**:964-966, 1954.
90. Fischer, F., and Hastrup, B.: Cortisone and Calcium Balance (Effect of Calcium, Vitamin D and Methyl Androstenediol), Acta endocrinol. **16**:141-148, 1954.
91. Zondek, B.: Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation, Baltimore, 1941, Williams & Wilkins Company, pp. 30-37.
92. Reifenstein, E. C., Jr., and Albright, F.: The Metabolic Effects of Steroid Horomones in Osteoporosis, J. Clin. Invest. **26**:24-56, 1947.
93. Henneman, P. H., and Wallach, S.: A Review of the Prolonged Use of Estrogens and Androgens in Postmenopausal and Senile Osteoporosis, A.M.A. Arch. Int. Med. **100**:715-728, 1957.
94. Perloff, W. H., Boutwell, J. H., and Maas, R.: The Endocrine Treatment of Climacteric (Steroid Deficiency) Osteoporosis, J. Am. Geriatrics Soc. **4**:760-765, 1956.
95. Cofer, E. S., Porter, T., and Davis, M. E.: The Effect of Withdrawal of Estrogens on the Nitrogen, Calcium and Phosphorus Balances of Women, J. Nutrition **61**:357-371, 1957.
96. Gordan, G. S.: Evaluation and Use of Anabolic Steroids, G. P. **10**:87-102, 1954.
97. Whedon, G. D., and Shorr, E.: Metabolic Studies in Paralytic Acute Anterior Poliomyelitis. IV. Effects of TP and Estradiol Benzoate on Calcium, Phosphorus, Nitrogen, Creatine and Electrolyte Metabolism, J. Clin. Invest. **36**:995-1018, 1957.

The effects of narcotics and antagonists upon respiration and circulation in man

A review

The respiratory response of normal man to therapeutic doses of narcotics is a diminution in alveolar ventilation primarily as a result of a decrease in tidal exchange. The alterations in respiratory rate and in alveolar ventilation in the subject breathing room air may be so subtle as to escape detection. A more reliable index of respiratory action of narcotics can be gained from a measurement of alveolar and arterial carbon dioxide tension. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. While a depression of the respiratory center sensitivity to carbon dioxide or hydrogen ion stimuli appears to be the principal cause of the diminished alveolar exchange from narcotics, it is probably not the only one.

The action of narcotics upon respiration is antagonized by pain and by nalorphine and levallorphan, although the latter drugs resemble narcotics in their effects if given to nonnarcotized patients. Mixtures of narcotics and antagonists given to normal subjects depress respiration as much as, or slightly less than, the narcotic alone. However, mixtures injected in patients who have had a narcotic may fail to cause respiratory depression. The respiratory effect of narcotics is enhanced by pulmonary disease, old age, chest deformities, general anesthetics, and phenothiazine drugs.

The principal effect of narcotics upon the circulation seems to be hypotension. This is caused by vasodilation and peripheral pooling of blood. It is partly explained by a release of histamine and in part by undefined central effects. The combination of narcotic with an antagonist may not be effective prophylaxis for hypotension from the narcotic.

James E. Eckenhoff, M.D., and Steffen R. Oech, M.D. *Philadelphia, Pa.*
Department of Anesthesiology, University of Pennsylvania Schools of Medicine

This review has been prepared in an effort to summarize, correlate, and interpret the available data concerning the actions of narcotics and the narcotic antagonists on respiration and circulation in man. The number of papers concerning this topic is extraordinarily large. On the other hand, those reports that permit accurate interpretation are surprisingly few. Most of the articles summarize clinical experiences with a new proprietary narcotic, usually claiming good analgesic effectiveness with minimal side reactions. Such studies commonly have no standard of comparison, few are

objective, and rarely are they critical. Review of such reports would serve little purpose. Nor will an attempt be made to survey the literature prior to 1941 except in those instances where earlier work is appropriate to the discussion. An analysis of the actions of narcotics including nearly ten thousand references was published by Kreuger, Eddy, and Sumwalt[136] in 1941. Eddy, Halbach, and Braenden[68] have summarized the actions of the synthetic narcotics in 1956, and Schaumann[204] and Reynolds and Randall[190] have compiled volumes on morphine and morphine-like synthetics in 1957.

Throughout this review, no attempt will be made to compare the respiratory and circulatory depressant effects of different narcotics except where authors themselves have done this. The reasons are twofold: First, all narcotics of clinical value as analgesics are respiratory depressants and may be vasodepressor as well. Although the degree of depression may vary from one drug to another, the degree of depression is dependent upon the dose used, the route and speed of injection, and the condition of the subject or patient to whom the drug is given. Second, there are too few comparative studies and the ones published compare only several drugs. There seems little validity in assembling facts and figures from the effect of narcotics on respiration when differing doses have been given by variable routes to normal and ill subjects and with different parameters measured. This is not to say that one cannot contrast narcotics in this respect but rather that a valid relative scale is not obtainable at this time. Eddy, Halbach, and Braenden[68] have compared the respiratory effects of narcotics available through 1956 but only in so far as they are greater or less than morphine or codeine. However, when possible morphine and meperidine will be contrasted since they may be considered prototypes of two structurally different drugs and because the comparative side effects of the two groups do not seem clear in the minds of clinicians.

Respiration

How should data concerning the respiratory effects of narcotics in man be recorded to be most meaningful? Familiarity with the variety of factors involved in the control of respiration is a prerequisite. As Slome[215] has pointed out: ". . . the rate, rhythm, and depth of breathing may be modified from the higher centers in the brain, by reflex afferents from the respiratory tract, cardiovascular system, abdominal and pelvic viscera, skeletal muscle and joints, and organs of special sense and indeed from most organs and tissues of the body. Thus the activity of the central respiratory mechanism is affected by afferent impulses which enter the central nervous system along all the sensory cranial nerves and the spinal nerves as well as by the afferents from supramedullary levels—thalamic and hypothalamic nuclei—and from respiratory areas of the cerebral cortex.

"Some of these reflex effects are operating continously and are concerned with the maintenance of the normal rhythm of automatic respiration; others are employed in the correlation of the pulmonary ventilation to the ever-changing metabolic needs of the body for adequate oxygen supplies and for the effective elimination of carbon dioxide. Certain of these reflexes adjust the respiratory rhythm to changes in venous pressure and arterial blood pressure and others to changes in body temperature. Some form part of the intricate mechanism ensuring increased pulmonary ventilation when muscles are exercised, yet others seem to modify the pulmonary ventilation to maintain the constancy of the reaction of the blood and tissue fluid.

"It must be emphasized that normally these reflex effects are all integrated and that the activity of the respiratory center is determined by the sum of all the nervous and chemical factors, some excitatory and some inhibitory, which play upon the center. In this way the rate and rhythm of respiration, though under occasional voluntary modification, is continuously adjusted reflexly to subserve a large number

of varied and important functions in the maintenance of the constancy of the internal environment of the body."

Any study in man of the influence of narcotics on respiration is therefore applicable only to the circumstances under which the measurements were made. Data obtained from an apprehensive, physically tired, ill, anesthetized, or structurally abnormal individual as well as one in pain must be interpreted in light of the subject's mental and physical condition. Influences such as these may account in part for the variable incidence of side actions to narcotics which has been reported. Keats and Beecher[128] have appraised the situation as follows: "The data presented reflect the enormous individual variation in response to narcotics. Not only were there large differences between individuals in response to the same drug but also the severity of different side actions varied in single subjects. The importance of rigid controls and sound experimental design in such studies is obvious. It emphasizes the difficulties if not the impossibility of collecting side action data on hospitalized patients where such controls usually cannot be applied."

Assessment of respiratory depression has been attempted under a variety of conditions and by differing criteria. The most common method was to measure the response of respiratory rate, with or without respiratory minute volume, in patients given narcotics for the relief of pain or in those scheduled for operation. Others have obtained the same data from pain-free convalescent patients or normal volunteers. Information recorded by measuring these parameters only is inadequate and may be misleading. More definitive data have been accumulated by measuring tidal volume as well as rate and minute volume, by analyzing end-expiratory air for carbon dioxide content, and by challenging respiration through having the subject inhale mixtures of carbon dioxide. For this purpose carbon dioxide has been inhaled as a single standard concentration for a predetermined period of time, by the inhalation of several concentrations of carbon dioxide to provide a spectrum of response, or by the endogenous accumulation of carbon dioxide in a circle rebreathing system. These techniques have been refined by Lambertsen and Wendel[137] to one of stimulating respiration at the same end-expiratory carbon dioxide tension before and after administration of the test drugs rather than by the inhalation of known or unknown concentrations of carbon dioxide. The application of the carbon dioxide stimulating test has yielded considerable information.

It appears reasonable to conclude, therefore, if comparative tests are to be made, the most reliable respiratory studies of drug action are obtained in normal man, free of pain and apprehension, isolated from extraneous interference, and subjected to as rigid control as possible. Data accumulated under other circumstances must be considered supplemental and not substitutive information. Minimal information recorded should include respiratory rate, tidal and minute volumes, alveolar P_{CO_2}, and respiratory response to a carbon dioxide stimulus.

Narcotics characteristically lead to a diminution in alveolar ventilation. This could be accomplished by a reduction in respiratory rate, in tidal volume, in minute volume, or by an increase in anatomic or physiologic dead space.

Respiratory rate. The classical effect of large doses of narcotics is to reduce respiratory rate. This occurs with meperidine as well as with morphine. The slow, deep respirations of narcotic overdosage are so characteristic as to be of differential diagnostic value in establishing the etiology of poisoning. Therapeutic doses of narcotics do not always cause slowing of respiratory rate. Dripps and Comroe[49] gave 10 or 15 mg. of morphine intravenously to 26 subjects between the ages of 19 and 88 and noted a 22 per cent average maximal reduction in rate within 7.4 minutes. The rate gradually increased and by 20 minutes was only 4 per cent below control levels. Comparing this group with another 23 subjects given 10 to 20 mg. of morphine intramus-

cularly, they observed an average of 3 per cent depression in rate in 3 to 7 minutes increasing to 12 per cent in 26 to 30 minutes. Denton and Beecher[45] also saw a slight but statistically significant decline in respiratory rate in one series of patients experiencing pain and another of normal volunteers given morphine (10 mg. per 150 pounds) and two methadone derivatives. Loeschke and associates[146] gave saline, morphine (10 mg.), and meperidine* (150 mg.) intramuscularly to normal subjects and did not observe a slowing of respiratory rate when the subjects breathed room air. When breathing was stimulated with carbon dioxide a statistically significant difference from control value was apparent only in the subjects given meperidine. In a study of the effects of seven different narcotics given in therapeutic doses,[61] a depression of respiratory rate was observed in only 6 of 21 normal subjects, there was no change or an equivocal change in 11, and the rate increased in 4. Morphine did not lower the rate in any of 4 subjects to whom it was given. Orkin, Egge, and Rovenstine[173] noted that 10 mg. morphine intravenously in patients scheduled for operation produced a 10 to 15 per cent slowing of respiratory rate in 5 minutes with a persistence at this level for 20 minutes and a return toward normal in the next 20 minutes. Meperidine, 100 mg. intravenously, produced a sustained increased in rate of 10 to 15 per cent. Huggins and co-workers[117] gave morphine intravenously in 15 mg. increments (time interval not stated) to convalescent patients and noted, "Morphine up to 60 mg. produced little change in the average respiratory rate."

These data suggest that the effects of therapeutic doses of narcotics on respiratory rate is not marked if the drugs are administered subcutaneously or intramuscularly. If the drugs are given intravenously, depression of respiratory rate may occur, reaching a maximum shortly after injection and returning toward control levels fairly rapidly. There is thus little support for the common clinical practice of observing a patient's respiratory rate as an index of when additional doses of narcotics can safely be given.

Tidal and minute volume. Data on the effect of narcotics upon respiratory tidal volume and minute volume are likewise not uniform unless the subject's breathing has been stimulated by the inhalation of carbon dioxide. With therapeutic doses of narcotics and with subjects breathing room air, 100 per cent oxygen, or a combination of nitrogen with greater than 20 per cent oxygen, a slight diminution in tidal and minute volume has generally been observed. Loeschke and associates,[146] Huggins and co-workers,[117] Dripps and Comroe,[49] and Eckenhoff and associates[61] noted a decrease in both measurements with intravenous or intramuscular doses of morphine up to 20 mg. Orkin, Egge and Rovenstine[173] recorded a suprisingly small change in tidal volume except for a transient reduction lasting less than 10 minutes with the intravenous injection of 10 mg. morphine in patients immediately prior to operation. They noted, however, a persistent decrease with alphaprodine* and meperidine, most marked with 100 mg. of the latter drug. Huggins and associates[117] recorded a progressive and marked reduction in minute volume as increments of 15 mg. of morphine (time interval not stated) increased the total dose to 90 mg. The depression in tidal volume, however, seemed to reach a plateau after 30 mg. morphine.

The diminution in tidal volume from a therapeutic dose of narcotics is therefore not of great magnitude in the normal individual breathing oxygen or room air and in fact may be sufficiently small to be overlooked. Having the subject breathe various concentrations of carbon dioxide increases the likelihood of detecting narcotic-induced respiratory depression. This is not a new

*Demerol.

*Nisentil.

thought, having been first applied to the study of narcotics in 1890 by Loewy.[148,149] From a clinical point of view, the test mimics the circumstances of increased arterial tensions of carbon dioxide such as occur during respiratory depression, asphyxia, and respiratory obstruction.

Prescott, Ransom, Thorp, and Wilson[183] have used *only* the response to the inhalation of carbon dioxide as an index of comparison of the respiratory depressant effects of narcotics in normal volunteers. The subjects breathed 5 per cent carbon dioxide in oxygen for 6 minutes and recordings were made every 30 minutes for 3½ hours after the intramuscular injection of morphine 10 mg., meperidine 100 mg., or methadone 10 mg. Morphine depressed the respiratory response to carbon dioxide to a maximum of 66 per cent of control readings, meperidine to a maximum of 59 per cent, and methadone to a maximum of 61 per cent. At the end of 3½ hours, the respiratory response to carbon dioxide had returned to 91 per cent of control with all three drugs. Considering the depression of response caused by morphine as 1, that produced by methadone was 0.93, and that from meperidine was 1.17, indicating that meperidine in the dose used was more depressant to respiration than was morphine.

On the basis of both control respiratory studies as well as stimulation of respiration by 4 per cent and 6 per cent carbon dioxide, Loeschke, Sweel, Kough, and Lambertsen[146] concluded: ". . . the dosage of meperidine required to equal the respiratory depressant effects of 10 mg. morphine would have been about 75 mg., since the effects of 150 mg. of meperidine (used in the study) were about twice those of morphine." Subsequently, Wendel and Lambertsen[254] studied the action of 5, 10, and 15 mg. morphine per 70 kilograms and 50 and 100 mg. meperidine per 70 kilograms upon respiration in groups of 6 to 8 healthy men. The observations were made at a constant "alveolar" Pco_2 of 46 mm. Hg.[137] They concluded: "Comparison of the two dose effect curves reveals that 25, 56, 82, and 106 mg. meperidine hydrochloride are as depressant to respiration as 5, 10, 15, and 20 mg. morphine sulfate, respectively, indicating an average potency ratio of 5.4:1 for morphine to meperidine. Since the analgesic potency of morphine is 8-10 times that for meperidine, the therapeutic index (respiratory depressant potency/analgesic potency) of meperidine is only about 0.6 that of morphine, and in equi-analgesic doses meperidine depresses respiration about 1.3 times as much as morphine."

Eckenhoff, Helrich, Hege, and Jones[61] have presented data from 21 normal volunteers given morphine 10 to 15 mg., dihydromorphinone 2 to 3 mg., meperidine 60 to 125 mg., methadone 7.5 to 8 mg., alphaprodine 45 to 60 mg., codeine 60 mg., and racemorphan* 5 to 7.5 mg. intramuscularly. Depression of the respiratory response to endogenously accumulated carbon dioxide was evident in all subjects. No attempt was made to average the observed depression nor to compare the effects of the different drugs.

Becker, Nassr, and Schwab[13] recorded the effect of morphine 10 mg. and racemorphan 2 mg. intramuscularly in 6 and 5 normal subjects, respectively. They observed little change in respiratory rate but saw a pronounced reduction in respiratory minute volume after morphine. The change with racemorphan was negligible until respiration was stimulated with carbon dioxide. A marked depression in minute volume became apparent with both drugs with this stimulus. The depression of respiration by morphine was statistically significantly greater than that for racemorphan.

Eckenhoff, Helrich, and Rolph[64] using endogenously accumulated carbon dioxide in 5 normal subjects given 50 to 60 mg. dihydrocodeine intramuscularly concluded that the depression of respiratory response to carbon dioxide "was less than that observed in two subjects following the injection of 60 mg. of codeine sulfate." However, Seed, Wallenstein, Houde, and Bellville[209]

*Dromoran.

studied the effects of morphine and dihydrocodeine on the respiratory response to carbon dioxide and compared the displacement of alveolar ventilation–alveolar P_{CO_2} response curves. They concluded that 77 mg. dihydrocodeine was as depressant to respiration as was 10 mg. morphine.

Chang, Safar, and Lasagna[32] compared the respiratory depressant effect of anileridine* and meperidine. Stimulating respiration with 5 per cent mixtures of carbon dioxide, they could detect no difference between the depression produced by 100 mg. meperidine and 60 mg. anileridine. Appreciably diminished response was apparent from both drugs, however.

The duration of the respiratory depressant activity of narcotics does not appear to have been studied adequately. The response to a carbon dioxide stimulus would again seem to offer the best evidence of persistent depression. Prescott, Ransom, Thorp, and Wilson[183] observed that in 3½ hours, the respiratory response to carbon dioxide in normal volunteers had returned to about 91 per cent of normal after 10 mg. morphine, 100 mg. meperidine, or 10 mg. methadone intramuscularly. Eckenhoff, Helrich, Hege, and Jones[61] noted a depression of respiratory response to carbon dioxide exceeding 4 hours in normal subjects given 15 mg. morphine and methadone 8 mg. intramuscularly. The diminution exceeded 5 hours in subjects given 125 mg. meperidine and 3 mg. dihydromorphinone.† Other side effects of narcotics such as nausea, lack of appetite, and dysphoria were noted to last long after the final recording of respiratory data. Keats, Telford, and Kurosu[131] observed the depression of respiration from 40 mg. anileridine to last 3 hours and from 100 mg. meperidine to exceed 4 hours. Lambertsen and Wendel[137] recorded that respiratory depression, as judged from the carbon dioxide stimulus, from meperidine 100 mg. per 70 kilograms intramuscularly in normal subjects, had declined to one half its maximal value in 4 hours. The respiratory effect of 60 mg. codeine has likewise been noted to exceed 4 hours.[15] Data from these sources indicate that respiratory depression from therapeutic doses of narcotics injected intramuscularly may exceed 4 to 5 hours.

Pulmonary dead space. Few measurements of the influence of narcotics upon either anatomic or physiologic dead space have been made. Morphine is generally considered to be bronchoconstrictor although data to support such an effect in man are not extensive.[2,108] If the drug has this effect, one should expect a diminution in anatomic dead space. Meperidine, on the other hand, is reputed to be bronchodilator[70]; therefore it should increase anatomic dead space. Here again confirmatory data from man are scanty. There are indeed several suggestions that meperidine is capable of producing bronchconstriction.[152,166] Recent observations by Shemano, Wendel, and Katinsky[212] indicate that, in the intact dog, meperidine injected intravenously in concentrations ranging from 0.5 mg. to 2.5 mg. per kilogram produces bronchoconstriction. At the latter concentration, the constrictor effect was marked, was apparent in every dog in which the drug was injected, and was indistinguishable from that produced by morphine. Also of interest are the observations of Cooper and Lambertsen[38] that P_{CO_2} elevations per se can increase the pulmonary dead space. Since the narcotics appear able to alter dead space and to lead to an increase in end-expiratory P_{CO_2}, it might be difficult to separate the individual effects.

It is apparent that more data are required to delineate the effect of narcotics upon bronchial caliber and pulmonary dead space. It is of note that in 1915 Higgins and Means[108] wrote: "While most workers have made some allowance for change in respiration rate in interpreting an increased respiratory volume, none seems to have considered all the factors involved and their interrelation. The possibilities of changes in the

*Leritine.

†Dilaudid.

gaseous metabolism and in the bronchial musculature seem to have been especially overlooked. . . . Any change in the tone of the bronchial musculature, leading to a change in volume of each respiration, as the result of a larger or smaller 'dead space,' may make considerable variation in a minute's respiratory volume and is a factor which has been generally overlooked by investigators, a changed ventilation following the administration of a drug having been usually attributed solely to action on the respiratory center." Although there is currently an awareness of the possibilities of change in bronchial caliber influencing the study of the respiratory effects of narcotics,[220] there have been few measurements of this parameter although the means to make such measurements are at hand. Since the response of alveolar Pco_2 is the same with both morphine and meperidine, one suspects that an alteration in dead space is not a prominent feature of either or that whatever effects on dead space are produced by the drugs are negligible in contributing to the rise in alveolar Pco_2.

Elevation in alveolar Pco_2. Narcotics usually lead to an elevation in end-expired Pco_2 and therefore in arterial Pco_2. The increase parallels the degree of respiratory depression. Higgins and Means[108] observed that in their subjects the elevation in Pco_2 followed the onset of decreased pulmonary ventilation. Loeschke and associates[146] noted a mean rise of alveolar Pco_2 of 2.6 mm. Hg following 10 mg. morphine in 6 subjects and 3.9 mm. Hg rise in the same subjects when given 150 mg. meperidine. Eckenhoff, Helrich, Hege, and Jones[61] recorded a rise of 2 to 13 mm. Hg in end-expired Pco_2 in 21 normal subjects given a variety of narcotics. Becker, Nassr, and Schwab[13] noted that alveolar Pco_2 rose from 38.7 $\pm$ 0.9 to 40.4 $\pm$ 0.3, 45 minutes after the intramuscular injection of 10 mg. morphine while 2 mg. racemorphan increased the level from 38.0 $\pm$ 1.76 to 40.3 $\pm$ 0.77. Six subjects were studied in each group. Huggins, Spencer, Geddes, Deavers, and Moyer[117] saw a slight decrease of Pco_2 with 15 mg. morphine followed by a progressive rise of 20 per cent as increments of 15 mg. morphine were increased to a total of 90 mg. Eckenhoff, Helrich, and Rolph[64] observed 50 or 60 mg. dihydrocodeine intramuscularly to increase the end-expiratory Pco_2 2 to 6 mm. Hg in 5 normal male subjects. Seed and associates[209] calculated that 5 mg. morphine subcutaneously led to a 2.18 mm. Hg increase in alveolar Pco_2, 10 mg. morphine to 4.85 mm. Hg rise, and dihydrocodeine 30 and 60 mg. to 2.10 and 3.47 mm. Hg rise, respectively.

Mechanism of respiratory depression. The precise mechanism by which narcotics decrease minute and tidal exchange is not clear. Carbon dioxide tension or hydrogen ion concentration directly affects the respiratory center and narcotics diminish the response of the center to the carbon dioxide stimulus. Is this the only significant respiratory effect of narcotics? There are opinions that it is only one of several possible mechanisms of action. Others that have been proposed include a diminished sensitivity to the reflex effects of sensory stimuli,[35,103,111] by an action altering body metabolism,[135] and by changes in the cortical response to carbon dioxide which indirectly influences respiration.[41,42,189,204,207] An interference by narcotics with the circulation to or from the respiratory center might also explain part of the respiratory action but, as will be discussed, no significant direct effect of morphine on the cerebral circulation has been found.[151,169] While there are no precise definitions of these possible mechanisms, some of the data relative to them must be considered.

Perhaps the part played by stretch and chemoreceptors has been studied most carefully. Liljestrand,[144] reviewing the neural control of respiration, concluded, "The peripheral chemoreceptors . . . exert a certain tonic reflexogenic stimulation on respiration, so that a selective elimination of them causes a reduction in pulmonary ventilation. Thus the chemoreflex component is an essential factor in the finer adjustments

of respiration with regard to carbon dioxide." However, there are no data from man suggesting that narcotics can depress these peripheral chemoreceptors. Gruhzit[96] presented evidence from dogs and cats to show that morphine stimulated pulmonary chemoreceptors, but von Euler and Soderberg[71] found in cats that these reflexes were nearly unaffected by a chloralose concentration sufficient to block the central effect of carbon dioxide. They also found that morphine failed to influence peripheral chemoreceptors yet depressed receptors in the respiratory center believed sensitive only to carbon dioxide. Breathing 100 per cent oxygen inactivates certain chemoreceptors,[157] yet there are no data to indicate that oxygen alters the respiratory response to narcotics as seen with room air, except in the presence of hypoxia.[51] That such an effect might occur should not be overlooked so that in respiratory studies, control and test measurements should be made with the subjects breathing concentrations of oxygen which are least likely to affect chemoreceptors, i.e., 50 per cent or less.

The possibility that narcotics alter pulmonary stretch receptors has apparently not been investigated in man although there are data to suggest they enhance Hering-Breuer reflexes in the cat.[158] The professed ability of normal subjects and patients to breathe easier after narcotics and their indifference to respiration suggest such an influence, although this could be a cortical influence as well. The loss of voluntary control of inspiration in patients under the influence of large doses of narcotics, yet with the retention of the ability to breathe when commanded to do so could have a similar meaning.

Data implicating the higher centers in the control of respiration in normal man are meager, yet there are facts to be considered. If these centers are depressed, as during sleep, a change in respiration is apparent. Most narcotics act as sedatives. If this effect is pronounced and the patient or subject sleeps, the pattern of respiration ensuing is that of respiratory depression. Bellville, Howland, Seed, and Houde[14] have observed that natural sleep per se can mimic the effects of narcotics so far as respiration is concerned. Studying normal volunteers in various "depths" of natural sleep, whose respiration could be stimulated at will by endogenously accumulated carbon dioxide, they noted a lowered respiratory exchange, an increase of end-expiratory Pco_2, and a diminished respiratory response to carbon dioxide. They observed: "There was a profound shift of the respiratory response curves to the right during moderately deep sleep which was greater than that produced by 10 mg. morphine sulfate given intramuscularly." They also made the important observation that narcotics could produce a similar respiratory effect without an alteration in the state of wakefulness. Others[189,195] have studied respiration during sleep and have noted the elevation in end-expiratory Pco_2,[194,188] but none appear to have compared the effect directly with that produced by narcotics. It seems likely, therefore, that sleep induced by narcotics during respiratory studies may confuse the results. There are no data, however, to indicate that the effect of sleep and of narcotics upon respiration are additive. Nor do the results reported above agree with the failure to observe respiratory depression or elevation in end-expiratory Pco_2 during sleep induced by secobarbital[61] or chloral hydrate.[149]

Occasionally narcotics induce a state of restlessness. Frequent shifting of body position may lead to deep inspirations and other irregularities of respiration sufficient to mask depression and, under these conditions, may even suggest an enhancement of respiration by the narcotic. Restlessness is more likely to be seen following the injection of narcotics in normal subjects or pain-free patients than in patients who have required pain relief. Therefore, it would seem reasonable to consider restlessness an unusual response to narcotics, and data accumulated under these circumstances might be segregated from that obtained during the more normal response.

Breckenridge and Hoff,[21,22] observing in dogs and cats the alteration of respiration produced by narcotics, concluded that these drugs might cause "pharmacologic decerebration." The common appearance of irregular and periodic breathing after morphine[111] was considered an inactivation of cortical and subcortical suppressor mechanism. The ability of narcotics to produce irregular and periodic breathing in normal man is less well appreciated but nevertheless seems to be common. Orkin, Egge, and Rovenstine[173] note that 9 of 10 patients given alphaprodine 60 mg., 7 of 10 patients given meperidine 100 mg., and 6 of 10 patients given morphine 10 mg., intravenously, developed periodic breathing. Those patients who had the greatest depression of cerebral functional activity manifested the most marked periodicity. Although not commented upon by the authors, Eckenhoff, Hoffman, and Dripps[65] presented spirograms from 2 patients, one who had received 100 mg. Pantopon and the other 6 mg. dihydromorphinone and both patients showed markedly irregular respiration. If it is accepted that morphine might produce "pharmacologic decerebration" in animals, leading to irregular respirations, it must be concluded that the same phenomenon occurs in man.

When narcotics are given to the very ill or the elderly, a more profound effect upon respiration often occurs than seen in the healthy individual. Likewise when narcotics are given in the presence of anesthesia, an exaggerated respiratory depressant response usually follows. These observations suggest that under the conditions mentioned a compensating mechanism to ensure adequate respiration after narcotics has been removed. Could this be a reduction in sensory input which helps to maintain respiration?

The importance of sensory input in the maintenance of normal respiration is the most poorly defined of the possible influences. Nevertheless, it is apparent that sleep and anesthesia mentioned above do reduce sensory input. Phenothiazine derivatives, although they do not appear to exert much effect on respiration per se, are known to diminish sensory input and do augment the effects of narcotics on respiration (see later discussion). Additional suggestions of the influences of sensory input upon respiration are obtainable from patients under the influence of spinal anesthesia. When sensory anesthesia extends to the upper thoracic region (T_4 and above), patients commonly complain of an inability to breathe even though respiration appears to be normal and exchange more than adequate. Sometimes the complaint is described as a heaviness of the chest or a weight on the chest. Macintosh[153] has called attention to the fact that the higher a spinal anesthetic spreads, the more awareness of the body is diminished. In the reviewers' opinion, the diminished awareness is responsible for the lack of appreciation of adequate respiration. If, now, thiopental* is injected intravenously in a dose sufficient to produce sleep but not normally depress breathing, respiration may suddenly cease with the onset of sleep. This is especially common if the patient has had a preanesthetic narcotic. It would appear as if respiration were being maintained by consciousness and, when consciousness is lost, respiration may cease. The suggestion is apparent that, at least under certain circumstances, afferent stimuli from the thorax or body, independent of the phrenic nerve, have much to do with the adequacy of respiration. Narcotics might mimic in part the action of a spinal anesthetic. Little work in defining the importance of sensory input in influencing normal respiration appears to be in progress.

Probably the degree to which afferent stimuli participate is determined by their importance in maintaining respiration in a given situation. When cortical control of respiration or sensory input to the respiratory center is blocked by anesthetics, the respiratory-depressant effect of narcotics is more prominent. If sensory input is re-

*Pentothal.

duced by disease, local anesthetics, or other drugs, again the narcotics seem to have more than expected respiratory action. Finally when the lungs or thoracic cage are affected by disease or congenital abnormality, serious respiratory depression may follow the injection of narcotics.

From the foregoing discussion, the respiratory response of normal man to therapeutic doses of narcotics might be summarized as follows: There is a diminution in alveolar ventilation, primarily as a result of a decrease in tidal exchange. The alterations in respiratory rate and in alveolar ventilation in the subject breathing room air may be so subtle as to escape detection. A more reliable index of respiratory action of narcotics can be gained from a measurement of alveolar or arterial carbon dioxide tension which is usually elevated, and through challenging respiration by inhalation of mixtures of carbon dioxide in 50 per cent oxygen. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. While a depression of the respiratory center sensitivity to carbon dioxide or hydrogen ion stimuli appears to be the principal cause of the diminished alveolar exchange from narcotics it is probably not the only cause. A dampening of as yet ill-defined influences upon respiration of afferent impulses from the periphery and cortical centers may play a significant role.

Alterations in the normal respiratory response to narcotics. There are many circumstances that affect the action of narcotics on respiration, yet one cannot accept data from any of these as representative of "normal" response to narcotics. Perhaps one should regard a narcotic effect in the healthy subject as "base-line" and attempt to define those conditions under which such a "normal" response is altered. As Keats and Beecher[128] have pointed out, there is no reason to believe that the mechanism of side action production in normal man differs from that in ill individuals. If one could obtain a sufficient number of observations on the effect of narcotics in man afflicted with reasonably standard degrees of illnesses or under the influence of comparable amounts of different drugs, the "spectrum" of action of narcotics would be better defined.

Factors that tend to counteract respiratory depression.

A. PAIN. Pain is usually a potent stimulant to respiration. Henderson[104] envisioned the stimulus as being sufficient to produce acapnia and shock. The clinician administering narcotics to a patient in pain does not expect respiratory depression unless the narcotic relieves the discomfort. Patients with renal colic due to a calculus often show little response to large doses of narcotics until the calculus is passed into the bladder, at which time profound respiratory depression may occur. Similar responses have been noted with the relief of pain of tabetic crises.[231] The anesthetist makes use of the respiratory stimulant effect of pain during light planes of anesthesia as a guide for the administration of more analgesic or the provision of a deeper level of anesthesia. It is probable that with light planes of anesthesia such as during the administration of the nitrous oxide–thiopental–narcotic combination respiratory stimulation by subconscious pain perception may play a more significant role than is commonly appreciated. The importance is not so much during the operation when the patient is under the constant surveillance of the anesthetist but rather postoperatively when the pain of operation has lessened and the patient is observed only periodically. The apparent "reanesthetization" of patients who seemed responsive at the termination of operation can be explained partially on this basis. Hamilton and Devine[100] have recorded a high incidence of respiratory inadequacy in patients admitted to recovery rooms following the use of such combinations of anesthetics.

While the usual effect of pain upon respiration is one of stimulation, under certain circumstances it may cause a diminution in pulmonary exchange and narcotics may then lead to an improvement in

ventilation. Anscombe[4] has noted that pain can cause: (1) bronchospasm, (2) a reluctance to cough and to clear secretions from the airway, and (3) a resistance to movement lest pain be aggravated, all predisposing to pulmonary hypoventilation. These conditions occur especially after upper abdominal or thoracic operations. Anscombe and Buxton[5] have measured vital capacity under these circumstances, and noted a reduction of as much as 80 per cent after upper abdominal operations. They have observed that 10 to 15 mg. morphine, given 6 to 12 hours postoperatively, increased the vital capacity as much as 16 per cent compared to the effect of the same dose of drug in the same patient before operation. When the same dose of narcotic was given 24 hours later, the vital capacity was depressed as much as 9 per cent. Similar salutory effects of morphine upon respiration in the presence of the pleuritic pain of lobar pneumonia have been reported by Davis.[44]

Bromage[23] has described a method for assessing the analgesic effectiveness of drugs by measuring the improvement in vital capacity after narcotics in patients after operation. The patient's preoperative vital capacity is measured, compared with that obtained postoperatively when pain is present and again after the drug being tested has been given. The observations are compared with vital capacity measurements made during a sensory block of the painful area by means of local anesthetics injected epidurally.

Because of these variable effects of pain upon respiration, it should be recognized that data obtained under such circumstances are applicable only to the given situation.

B. EMOTIONAL STRESS. If "control" observations in a respiratory study are obtained in normal volunteers or patients who are apprehensive, fear discomfort, lack interest in the investigation, misinterpret sensations experienced, and are impatient to complete the work, the results of the study may not be valid. Subjects frequently find it difficult to distract their attention from breathing and may involuntarily hyperventilate or hypoventilate. Apprehension may elevate the catechol amine blood level which may indirectly affect respiration. Should the test drugs produce restlessness or dysphoria, studies of respiration may not be comparable to observations obtained from other subjects in whom the same drugs produced relaxation and euphoria. The attitude and conversation of the investigators and the atmosphere under which the experiment is conducted can also influence results.

The determination of respiratory response to narcotics in normal volunteers is probably no different so far as interference from emotional stimuli is concerned than the study of the analgesic effects of narcotics.[110] If such responses are common in normal volunteers, how much more common must they be in studies attempted on patients facing operation, incurable malignancy, or financial catastrophe. Great care must be exercised in obtaining both control and test data under these circumstances.

C. DRUGS. 1. Belladonna alkaloids. Many studies of the action of narcotics upon respiration have been conducted in patients given belladonna alkaloids before or simultaneously with the narcotic. Belladonna drugs cause bronchiolar dilatation and thereby increase anatomic dead space. Severinghaus and Stupfel[211] measured the effect on dead space of 0.5 mg. of atropine given subcutaneously in human subjects and observed a 30 per cent increase. When atropine 0.5 to 1.0 mg. was injected intravenously, there was a 47 per cent increase in dead space. Morphine and meperidine, on the other hand, seem to be bronchoconstrictors. What then is the effect on dead space when combinations of morphine and atropine are administered together? There are no reliable data. Steinberg, Bellville, and Seed[220] concluded that atropine counteracts the constrictor effect of morphine but supporting data are lacking.

Scopolamine has been alleged to have

respiratory stimulant properties and to be of value in counteracting the respiratory depressant effects of narcotics.[245,246,247] The evidence is not convincing. Loewy,[149] Loeschke and Wendel[147] and Weimann and Hermanuz[249] were unable to show that atropine or scopolamine stimulated respiration. Nor did Steinberg, Bellville, and Seed[220] find that 0.6 mg. atropine altered the respiratory depression produced by 10 mg. morphine. Atropine alone did not alter the respiratory response to endogenously accumulated carbon dioxide, nor did the combination of atropine and morphine alter the response curve obtained from morphine alone. Swerdlow and Newman[229] injected intravenously morphine (1/6 mg. per kilogram) with scopolamine or atropine in 100 patients. They observed that the mixtures had little effect upon respiratory rate but that both combinations depressed minute volume of respiration. One must conclude, therefore, that although there has been some belief that belladonna drugs counteract narcotic-induced respiratory depression, the available data do not support such opinion. Weimann and Hermanuz[249] believe that atropine added to dihydromorphinone provides more even alveolar ventilation through its bronchodilator effect. They came to this conclusion after administering 2 mg. dihydromorphinone and 0.3 mg. atropine to 8 normal subjects and noting that although alveolar ventilation diminished and $PAco_2$ increased, the physiologic dead space also decreased and the alveolar-arterial oxygen difference statistically was significantly diminished.

2. Narcotic antagonists. Several reviews of the pharmacology of narcotic antagonists have been published.[85,115,140,260] Two antagonists, nalorphine* and levallorphan,† are currently available for clinical use. They produce essentially similar effects, both in narcotized and normal man, although levallorphan appears to be about ten times as potent as nalorphine. Administered parenterally to normal man, nalorphine leads to a depression of respiration more or less paralleling that from equivalent amounts of morphine. Eckenhoff, Elder, and King[57] found that 5 or 10 mg. nalorphine injected intravenously in normal volunteers had little effect upon respiratory rate but led to a consistent diminution in respiratory minute volume averaging 35 per cent. Wikler, Fraser, and Isbell[257] gave 15 mg. nalorphine subcutaneously to 6 postaddict volunteers and failed to observe a significant effect upon respiratory rate during 3 hours of observation. Tenney and Mithoefer[237] saw a comparable effect in normal volunteers from 2 mg. nalorphine intravenously, and also demonstrated a diminished response to inhalation of carbon dioxide mixtures as compared to the predrug state. Lasagna and Beecher[141] decided that the respiratory depression from 5 mg. nalorphine in normal subjects did not differ significantly from that caused by 10 mg. morphine. Isbell and Fraser[119] observed irregularities in respiratory rhythm after 30 mg. nalorphine in postaddicts comparable to that seen after corresponding doses of morphine. Salomon, Marcus, Herschfus, and Segal[199] noted that the changes produced by 10 mg. nalorphine intravenously lasted from 40 to 90 minutes. Further studies with nalorphine and those with levallorphan have essentially agreed with the results already quoted.[62,117,227,238] It would appear from these data that both narcotic antagonists are depressant to respiration when administered intravenously, intramuscularly, or subcutaneously in normal man. Respiratory rate is either unchanged or slightly decreased, dependent upon the dose, and minute volume is nearly always lowered. Alveolar ventilation is diminished.

The ability of the narcotic antagonists to counteract respiratory depression produced by opiate derivatives and synthetic narcotics is well established. The intravenous injection of 5 or 10 mg. of nalorphine or comparable doses of levallorphan in a patient deeply narcotized and with marked respiratory depression will lead to one of

*Nalline.
†Lorfan.

the most dramatic reversals of drug action seen in medicine. Respiratory rate promptly increases as does respiratory minute volume, and the end-expiratory Pco_2 decreases toward normal. There are no data as to the optimal dose required to antagonize various degrees of respiratory depression caused by narcotics. Attempts have been made to determine such a relationship[80] but none could be found. Certain explanations for this will be offered later. The doses of antagonists most commonly used are nalorphine 5 or 10 mg. and levallorphan 1 or 2 mg. by vein. The duration of action of single doses has not been adequately measured, but the available reports suggest a duration of about 1½ hours for nalorphine and about 2 hours or longer for levallorphan.

The antagonists can also be used to counteract the depression of the infant's respiration by narcotics given to the parturient. Nalorphine, 10 mg. given intravenously to the mother 5 or more minutes prior to delivery, statistically significantly reduces the infant's respiratory depression.[66] A more direct method of treating narcotic-induced respiratory depression in the newborn is to inject 0.2 to 0.5 mg. nalorphine directly into the infant's umbilical cord vein. This produces excellent results if the depression is due to narcotics.[1,31,65,66,176]

The antagonistic effect of nalorphine and levallorphan appears to be specific for narcotics and does not extend to reversing depression produced by other substances such as anesthetics or sedatives.[1,57,139,162,199] Weakley and Bergner[248] gave 0.0625 mg. to 0.5 mg. per kilogram nalorphine intravenously to 18 patients anesthetized with secobarbital,* and noted that the respiratory depression from secobarbital was potentiated as judged by the respiratory rate and minute volume. Sleeping time was also prolonged. These data are supported by a comparable experiment in mice.[95] There has been, however, one report[54] claiming reversal of respiratory depression in 2 patients, one given 1.5 Gm. thiopental during extraction of all of his teeth and the other given 2.0 Gm. thiamylal* with nitrous oxide during a radical mastectomy. Large doses of nalorphine (35 and 40 mg., respectively) were used to effect reversal of barbiturate narcosis. There is no explanation for this single exception in man unless the patients might have been given narcotics preoperatively. Reports of comparable stimulation in dogs[242] and rats[39] narcotized with pentobarbital have appeared. Suggestions of a nonspecific stimulant action of nalorphine,[54] however, have not been substantiated by further work.[199] The presence of other cerebral depressants (e.g., ether) does not appear to hinder the action of antagonists if they are being used to counteract an effect caused by narcotics.[58,159]

The antagonists do not reverse narcotic-induced respiratory depression under all circumstances. The effectiveness of the antagonists appears directly related to the magnitude of depression caused by the narcotic. Landmesser, Formel, and Converse[139] have stated this somewhat differently, "The degree of initial hyperpnea following the administration of the narcotic antagonist is more dependent upon the amount of CO_2 that has been retained as a result of narcotic depression. . . ." The reviewers have not seen, nor are they aware of reports of, a single failure of the antagonists to reverse serious respiratory depression produced by narcotics. It is obvious that failure of reversal could occur if depression were complicated by the presence of other drugs, by trauma or disease, or by damage from hypoxia. On the other hand, there are frequent references to failure of antagonists to stimulate respiration after minor respiratory depression from narcotics. Eckenhoff, Hoffman, and Funderburg[66] noted that nalorphine seemed less effective in stimulating neonatal respiration if the mothers were lightly sedated

*Seconal.

*Surital.

from meperidine medication as compared with those who were moderately or deeply sedated. Wikler, Fraser, and Isbell[257] reported that nalorphine administered to patients with minimal depression might increase that depression. Payne[178] observed that 10 mg. nalorphine provided only a transient reversal of respiratory depression produced by 15 mg. morphine in healthy subjects. Lasagna and Beecher[141] recorded that the respiratory depression produced in 4 young healthy male volunteers by 15 mg. morphine and followed in 2 hours by 5 mg. nalorphine was not reversed in 3, and in the fourth the reversal was "short lived and was followed by more severe depression." Eckenhoff and Funderberg[58] presented data to show that "relatively large doses of antagonists may have minimal action if the degree of depression (respiratory) is minor," and noted that, "This supports the clinical observation that the opiate antagonists are most effective when the depression for which they are administered is greatest." Keats and Mithoefer[130] and Keats[127] have written that patients do not respond to nalorphine after a single therapeutic dose of morphine (at a time interval of one hour) unless a "priming" dose of morphine was given first. Fraser, Van Horn, and Isbell[87] observed that 10 mg. nalorphine given 1¾ hours after 30 mg. morphine in postaddicts did not affect the depression of respiration. Orton, Peacock, and Phillips[174] observed one subject given 10 mg. morphine intravenously followed in 22 minutes by another similar injection. A dose of 10 mg. nalorphine, 80 minutes after the first morphine injection, led to only a transient respiratory stimulation and a second injection of nalorphine 13 minutes later stimulated respiration sufficiently that the respiratory rate was still raised 70 minutes later.

Fraser[85] has summarized observations as outlined above as follows: "Nalorphine per se has a definite pharmacological action, and whether or not nalorphine acts as an antagonist for morphine depends upon a great many factors—doses of each and, most important of all, whether administration of nalorphine has been preceded by one, several, or an addictive dosage schedule of morphine. These divergent actions may be briefly illustrated as follows: a) In a dose of 10 mg. subcutaneously nalorphine depresses respiration and body temperature in a manner comparable to that of 10 to 30 mg. morphine. It provokes dysphoria in many subjects and it moderately constricts the pupils. b) When a single dose of 10 mg. to 20 mg. of morphine is followed one hour later by 10 mg. of nalorphine the latter will counteract to a considerable degree morphine-induced miotic effects and 'morphine euphoria,' but under these conditions will not counteract morphine-induced respiratory depression. c) If, however, the dose of morphine is sufficient to induce severe respiratory depression, then administration of 10 mg. of nalorphine promptly restores normal respiration."

The manner by which antagonists counteract respiratory depression produced by narcotics is not clear. The most popular theory is that the antagonists have a stronger affinity for respiratory center receptors than do morphine, meperidine, and the like.[84,85,140,192,210,260] If narcotics occupy the receptors, the antagonists displace them, thus substituting a milder respiratory depression that may simulate a return to normalcy. If the receptors are unoccupied as in the normal subject, the antagonists produce respiratory depression and prevent occupation by narcotics subsequently injected. This theory does not satisfy all circumstances, especially the fact that a mild respiratory depression may be unaffected or even intensified by the antagonist. As a result of this disparity, a theory has been developed envisioning physical dependence on narcotics as a prerequisite for the antagonistic action of nalorphine or levallorphan.[130,140,256] With this theory, dependence is established by the initial or "priming" dose of narcotic. This explanation seems unnecessarily complex to the reviewers. Is it not possible that with a therapeutic dose of narcotic leading to

minimal respiratory depression, the concentration of narcotic located in the respiratory center is so low, as a result of equilibration of the drug in body tissues and fluids, that the antagonist acts primarily as if no narcotic were present? It has been shown that both d-tubocurare[124] and thiopental[184,185] reach peak activity soon after intravenous injection with distribution in blood and extracellular fluid. A period of redistribution and equilibration then occurs during which time drug activity may diminish or disappear as drug concentrations decrease at effector organs. A final period of metabolism or excretion follows. While such a pattern has not been established for narcotics, there is little reason to doubt its occurrence. Marked respiratory depression must mean a high or relatively high concentration of narcotic at respiratory effector organs. Therefore antagonists are effective for indefinite periods after injection of large doses of narcotics or for short intervals after injection of smaller doses. When sufficient time has elapsed after therapeutic doses of narcotics and redistribution has occurred, the respiratory center concentration is low and a depressant (or transient stimulant) action of the antagonist is seen.

There are recent observations of antagonist action that do not appear to fit into the competitive receptor theory. Three independent groups have observed that respiratory depression produced by nalorphine can be reversed by subsequent doses of the same drug*† or of levallorphan.‡ The meaning of these observations is not clear.

So long as the antagonists do counteract severe respiratory depression, the fact that they are unreliable in reversing slight depression becomes of more academic than practical importance. The significant points are: (1) the antagonists should be reserved for the treatment of severe respiratory depression from narcotics, and (2) augmentation of depression may occur when antagonists are given to patients in mild respiratory depression.

Probably of more concern is a consideration of the antagonists injected prior to or simultaneously with the narcotic to prevent appearance of the side effects of narcotics yet preserve or augment analgesia. Since more data have appeared on the simultaneous injection of the drugs, this will be considered first.

Once the antagonism between morphine and nalorphine was demonstrated, attempts were soon made to combine both drugs to see if analgesia could be preserved and the side effects of the narcotic prevented.[172] The first data relative to such combinations in man appear to have been those of Cappe, Himel, and Grossman,[29] although Bodman[19] mentions that he gave 50 mg. meperidine with 3 mg. nalorphine to separate the analgesic and respiratory effects of the narcotic and concluded: "This seems to me to be a line worth pursuing." Cappe and associates[29] injected equal doses of nalorphine and morphine or one part nalorphine to 3 parts morphine in 45 parturients and observed only slight respiratory and circulatory depression in mothers and offspring. Later these authors[30] reported on 75 parturients given 5 to 40 mg. each of morphine and nalorphine (average 15.8 mg.) in equal amounts and noted that the effect on the mothers' respiratory rate, blood pressure, and pulse rate was negligible. Respiratory depression was observed in only one infant.

Investigation of mixtures seems to have been in two different types of subjects and the results have likewise differed. The subjects studied in the first group are volunteers, whereas the second consists of patients for whom an analgesic was indicated.

Volunteers: Lasagna and Beecher[141] gave combinations of nalorphine and morphine, in a 1:5 and 1:3 ratio, to normal young volunteers and observed that the side effects including respiratory depression were indistinguishable from those recorded after

*Keats, A. S.: Unpublished data.
†Gans, J. H.: Unpublished observations.
‡Eckenhoff, J. E., and Helrich, M.: Unpublished data.

the same doses of morphine alone. In these studies, respiration was stimulated with 5 per cent carbon dioxide mixtures. Eckenhoff, Helrich, Hege, and Jones[62] administered levallorphan and levorphan to normal subjects and challenged their respiration with endogenously accumulated carbon dioxide. They concluded, "In no instance was the mixture of levallorphan with levo-Dromoran in a dosage relationship of 1:1 or 1:10 capable of preventing the respiratory depression normally produced by levo-Dromoran." Thomas and Tenney[238] injected intravenously 1:5 mixtures of levallorphan and levorphan in healthy volunteers and challenged their respiration with carbon dioxide mixtures. The results were compared with those obtained in the same subjects given the same doses of each drug on separate occasions. They concluded, "When these two drugs are given together, ventilation is improved over that with either alone but it is still less than control." Fraser, Van Horn, and Isbell[87] studied the effects of morphine alone and in combination with nalorphine, injected subcutaneously in postaddict volunteers and concluded that morphine alone or with nalorphine depressed respiration in a comparable manner. Houde and Wallenstein[112] gave morphine combined with nalorphine on a 8:1, 4:1, 2:1, and 1:1 ratio to 38 hospitalized cancer patients. They concluded that "the incidence of volunteered and observable side effects increased in direct proportion to the amount of nalorphine in the mixture and in a separate limited study of the respiratory effects of the mixture in normal volunteers that the combination produced as much or more respiratory depression than morphine alone." Wallenstein, Bellville, and Houde[243] investigated the respiratory effects of intramuscularly injected levorphan and 0.3 mg. levallorphan, alone or in combination, in healthy volunteers. Respiration was stimulated with endogenously accumulated carbon dioxide. They concluded that 0.3 mg. levallorphan produced no significant respiratory depressant effect alone nor did it interfere with the depression produced by levorphan. Finally, Wendel and Lambertsen[253] gave nalorphine or morphine, 10 mg. per 70 kilograms each, alone or together, to 15 normal volunteers and stimulated their respiration with carbon dioxide mixtures. They noted that a synergism or an antagonism between the two could be observed but, in general, the combined effect of the drugs was not significantly different from that of morphine alone.

Patients requiring analgesics: The patients studied can be categorized as those with chronic pain[40,205]; those studied before and/or during anesthesia and operation[7,83,132,156,221,225,228]; those studied after anesthesia for a surgical procedure[160,161,198]; and those to whom the mixture was given prior to the birth of a child, the effect being observed on the infant's respiration.[10,25,84] The results of these investigations may be summarized by the generalization that the simultaneous injection of a narcotic (principally alphaprodine or meperidine) and narcotic antagonist (mostly levallorphan) has led to no more than slight respiratory depression as measured by respiratory rate, tidal and minute volume, or incidence of delayed onset of neonatal respiration. The ratio of narcotic to antagonist has varied but reasonable agreement of the following has appeared: morphine to nalorphine 3:1; levorphan to levallorphan 10:1; alphaprodine to levallorphan 50:1; and meperidine to levallorphan 100:1.

Only three clinical reports are at variance with those listed in the preceding paragraph. Two concern the use of the mixture in patients with chronic pain.[62,94] In the first of these,[94] "definite respiratory depression" was reported in 4 patients given levorphan and levallorphan mixtures, and in the second[62] respiratory depression is apparent in the data from 3 patients in pain given a 1:10 mixture of levallorphan and levorphanol with respiratory effect measured by analysis of rate, tidal volume, end-expiratory Pco_2, and response to endogenously accumulated carbon dioxide. The

prior experience of these patients with narcotics is not detailed. In the third report,[193] merperdine 150 mg. was given to 177 parturients with an additional 100 mg. if needed. Similar doses of meperidine, combined with 1 mg. levallorphan and 0.5 mg. if the subsequent dose of 100 mg. meperidine was given, were injected in an additional 178 parturients. The minute volume of respiration of the neonates was measured. The conclusion was drawn that levallorphan did not increase the infants' minute volume as compared with that of the controls and the incidence of fetal respiratory depression was the same in both series.

On the surface it is difficult to reconcile the observations from the volunteers and patient groups. A careful study of the conditions under which the investigations were performed in the patient group, however, suggests that nearly all if not all the patients had been given a narcotic for preanesthetic medication or had had previous injections of narcotics because of chronic pain. Although several authors specifically mentioned that their patients had not had narcotics for at least 7 to 8 hours prior to the study, nevertheless this could influence the results. The conditions, then, were different from those in most of the volunteers who have not had narcotic before the experiment and who presumably had not had prior experiences with narcotics for periods of days before the observations were made. If these assumptions are correct, then the different conclusions drawn from the two groups of investigation are explainable.

If the pattern of respiratory response is shaped by prior experience with either narcotic or antagonist, the question arises as to the need of injecting mixtures of the drugs. Why not inject the antagonist first and follow it at intervals with the narcotic as needed? Such a practice would be technically simpler and should be less expensive. The data suggest that when the drugs are given in this fashion and in the proper ratio, analgesia is preserved or enhanced[25,99,106,193] and respiratory depression is minimal. As will be discussed, however, the vasodepressor response to narcotics may not be blocked by antagonists used in this manner. It is interesting that antagonists can reverse one action of narcotics and augment other actions. Woods[261] has shown that nalorphine does not significantly alter the brain concentration of morphine even though the respiratory effects are prevented or reversed, and nalorphine slows, not hastens, the degradation of morphine in the rat liver.[8,9,155]

Hamilton and Cullen[98] injected intravenously 2.5 and 5.0 mg. levallorphan in patients scheduled for operation and anesthetized with nitrous oxide. This led to slight diminution in respiratory rate. Levorphanol, meperidine, or morphine, in doses calculated to produce definite respiratory depression (e.g., 18 mg., 400 mg., and 60 mg., respectively) were then injected. "The large doses of opiates did not produce the expected respiratory depression." It was also noted in those patients in whom respiratory depression from narcotics was antagonized with levallorphan, "additional doses of opiate as needed to supplement the anesthesia did not depress respiration." In a later publication, Hamilton and Cullen[99] used meperidine in combination with thiopental and nitrous oxide for anesthesia in patients undergoing minor surgical procedures. After the establishment of a satisfactory level of anesthesia, levallorphan was injected intravenously. This appeared to counteract respiratory depression as well as to lighten anesthesia. Subsequent doses of meperidine increased the level of anesthesia, yet allowed "only slight transient depression of respiration." Foldes and Ergin[83] have described a technique wherein patients who have received a narcotic for premedication are given 0.02 mg. per kilogram levallorphan intravenously, followed in 3 to 6 minutes by meperidine 2 mg. per kilogram, all prior to induction of anesthesia. A thiopental, nitrous oxide sequence is then given. Additional doses of thiopental or meperidine are used as needed but further doses of levallorphan are in-

jected only if respirations decrease below 12 per minute.

Foldes,[82] Coleman, Hargrove, and Jones,[36] and Foldes, Duncalf, Robbins, D'Sousa, and Conte[81] have used the antagonists in yet a different fashion. Foldes and associates[81] have injected alphaprodine, 1 mg. per kilogram in combination with narcotic premedication, thiopental, nitrous oxide, and succinylcholine* to produce apnea deliberately. At the end of the operation, the apnea is counteracted by the injection of 0.02 mg. per kilogram levallorphan. If respiration does not return satisfactorily, an additional 0.4 to 0.6 mg. of the antagonist is given. This procedure is called "controllable apnea." It is of interest that of the 531 patients reported upon, there were two deaths (one patient who had severe bronchospasm during and following operation had had 270 mg. alphaprodine; the other had a "low tidal volume" postoperatively and died 3 hours after completion of the operation). One additional patient gave great concern because her tidal volume remained below normal for 5 hours postoperatively.

The use of simultaneous or sequential injections of narcotics and antagonists has been confined chiefly to the treatment of acute postoperative pain or as an anesthetic adjuvant. Only two reports have appeared of their repeated use over a period of days. Eckenhoff and Norton[67] noted that after a patient with terminal carcinoma of the lung with metastasis had received 5 mg. levorphan with 0.5 mg. levallorphan for several days, pain was controlled but the patient became semistuporous and the medication had to be discontinued. Fraser, Van Horn, and Isbell[87] have described the administration of nalorphine-morphine mixtures (1:3, 1:10, 1:15) to postaddict subjects for periods of 30 days. "Patients liked these mixtures for the first two or three days, but thereafter progressively disliked them; because after several days, mild abstinence symptoms developed after each injection and the characteristic morphine-like euphoria did not materialize." They concluded that the mixtures might be satisfactory for treating acute pain but not for chronic pain.

The foregoing material may be summarized as follows: Mixtures of narcotics and antagonists given to normal volunteers depress respiration as much as or slightly less than the narcotic alone. When these mixtures are injected in patients who have had narcotic premedication or who have had recent prior experience with narcotics, however, respiratory depression fails to appear or is slight. A similar effect can be obtained by first administering a single dose of antagonist in order to block the respiratory depressant effects of subsequent doses of narcotics. The latter technique has more appeal to the reviewers. The use of mixtures of narcotic and antagonist does not seem applicable to the treatment of chronic pain.

3. Other respiratory stimulants. It is not in the province of this review to discuss the use of nonspecific analeptics or stimulants upon narcotic-depressed respiration. Several reports, however, deserve comment. Stroud, Lambertsen, and associates[223] studied the effects of a combination of meperidine and aminophylline upon respiration as well as that of aminophylline alone. They observed that 3 or 6 mg. per kilogram doses of aminophylline given intravenously increased the respiratory minute volume 46 and 98 per cent and believed that this was caused by an alteration of the central response to carbon dioxide. They also noted that if 150 mg. meperidine was injected intramuscularly at the same time 6 mg. per kilogram aminophylline was injected intravenously, respiration and the respiratory response to carbon dioxide was essentially unaltered. They concluded that aminophylline "neutralized" the depressant action of meperidine on the respiratory center. It is of interest that none of the other side effects of meperidine were alleviated.

Becker, Nassr, and Schwab[13] studied the

*Anectine.

effects of morphine and levorphanol upon respiration in 50 normal volunteers and compared the respiratory response of simultaneously administered combinations of the two narcotics with two theophylline derivatives, nikethamide,* and the narcotic antagonists. Aminophylline and nikethamide proved superior to the antagonists in preventing respiratory depression from the narcotics.

Factors that tend to augment respiratory depression from narcotics. The following discussion is an attempt to examine and define some of the factors that increase respiratory depression from narcotics.

A. DIMINUTION OF RESPIRATORY RESERVE. 1. Age. Because of the fear of respiratory depression, many physicians arbitrarily reduce the dose of narcotic in adults above 65 years of age. One of the reasons for an increased incidence of respiratory depression in this group is a diminished respiratory reserve. This is occasioned by an increase in dead space, a reduction in vital capacity, a limitation of chest wall excursion, and a higher incidence of chronic bronchitis with consequent accumulation of thick secretions. Tenney and Miller[236] have observed a 55 per cent increase in anatomic dead space in the elderly, probably as a result of relaxation of tracheal and bronchial walls. They have also noted a carbon dioxide gradient of 2 mm. Hg between alveolae and arterial blood which they believe is evidence for increased alveolar dead space. The tendency in the elderly toward the development of emphysema with a further increase in dead space is great. Monroe[168] recorded an incidence of pulmonary emphysema of 8 per cent in patients in the 61 to 65 year age group, increasing to 22.5 per cent in the 81 to 85 year age group.

The elderly compensate for these changes by an elevation of minute volume of respiration, primarily through an increase in respiratory rate. Tenney and Miller[235] observed respiratory rate and minute volume to increase from 11.4 per minute and 3.54 L. per minute in the third decade to 20.2 per minute and 5.9 L. per minute in the ninth. By this means alveolar Pco_2 levels are kept within normal limits. It is apparent, then, that the elderly person has called into play many of his compensatory mechanisms. If narcotics abolish or depress these compensations, a respiratory effect greater than usual might be anticipated. Morphine is more likely to depress an elevated respiratory rate than a normal one; tidal volume would be affected as it usually is but minute volume would be appreciably more reduced because of the diminished rate; bronchoconstriction, as presumably normally occurs, might be absent because of calcification of tracheal and bronchial rings; cough to clear secretions would be depressed and air flow would be impeded, adding to poorer alveolar ventilation. These alterations lead to less efficient dead space ventilation which hinders exchange of carbon dioxide and oxygen. While there are no data to indicate that the respiratory center of the elderly is less sensitive to carbon dioxide, there are reasons to suspect diminished responsiveness. As will be discussed, the emphysematous patient with a chronically raised alveolar Pco_2 is less sensitive to carbon dioxide stimuli. Kety[133] has noted a lowered cerebral blood flow, an increase in cerebrovascular resistance, and a diminution in cerebral oxygen consumption. These changes plus cerebral arteriosclerosis might interfere with the blood supply to the respiratory center sufficiently to impair that area's reactivity and augment the response to depressants.

There are no data on the relative incidence of narcotic-induced respiratory depression in the elderly as compared with other age groups. Such comparisons would be worth while. While most physicians accept as fact a higher incidence of such complication, there are some not so impressed. Schumann and McCall,[208] for instance, have been accustomed to injecting subcutaneously 15 mg. morphine with 1.2

*Coramine.

mg. scopolamine in elderly women for vaginal operations as the sole or principal anesthetic and observed "no problems." One would suspect that pain perception by the patient might act as a narcotic antagonist so far as respiratory depression was concerned.

The elderly vary in their response to depressant drugs. Probably a more accurate prediction of reaction of these patients is by their physiologic rather than chronologic age. One would anticipate that the elderly person who is physically and mentally active, who has minimal structural pulmonary changes, and who is not afflicted with chronic pulmonary disease such as bronchitis might respond no differently to narcotics than do most younger adults. The elderly might, however, require less narcotic for pain relief than the young, because their philosophical outlook on life makes them more tolerant of pain. On the other hand, it would be the inactive geriatric patient with chronic pulmonary disease or structural changes who might respond undesirably to a narcotic.

2. Pulmonary disease. Diseases of the lungs may reduce respiratory reserve and increase "sensitivity" to narcotics. Patients with pulmonary emphysema have been subjected to careful study and analysis. These studies have revealed a chronically elevated alveolar Pco_2, the elevation being directly proportional to the severity of the disease, and a diminished respiratory response to further elevations of carbon dioxide.[3,186,191,230,237,259] Dulfano, Mack, and Segal[54] postulated that, because of the elevated Pco_2, a narcotic antagonist should be a specific respiratory stimulant effective in treating respiratory acidosis under these circumstances. However, when Tenney and Mithoefer[237] investigated this possibility, they observed that nalorphine not only led to respiratory depression and elevation of Pco_2 but also further diminished the responsiveness of the center to a carbon dioxide stimulus. Wilson, Hoseth, and Dempsey[259] investigated the effects of morphine 10 mg. and of phenobarbital 60 mg. in a group of 26 patients with pulmonary emphysema and observed statistically significant respiratory depression, elevation of alveolar Pco_2, decrease in hemoglobin oxygen saturation, and decrease in arterial blood pH. They concluded: "In the patient with severe chronic pulmonary emphysema, these drugs are dangerous even in small doses because they depress the respiratory rate and lead to uncompensated respiratory acidosis. . . ."

Emphysema might be considered as one example of diseases that affect alveolae leading to an elevation of arterial Pco_2. Any other disease that interferes with alveolar ventilation and exchange of gases between alveolus and pulmonary capillaries would operate similarly. Response to narcotics would also be comparable.[182] Pneumonia is an additional example. Davis[44] gave 10 to 18 mg. morphine to 20 patients with lobar pneumonia and observed that arterial oxygen saturation declined in 16, the reduction averaging 5 per cent with a maximum of 21.3 per cent.

Bronchial asthma is another pulmonary disease in which patients respond poorly to narcotics; deaths following the administration of therapeutic doses of morphine to patients experiencing an asthmatic attack have been common.[120,239,241,244] While morphine has been the principal offender, meperidine does not seem to have been innocuous.[152,166] McDermott and Papper[152] have reported 6 case histories of anesthetized patients who have had asthmatic attacks precipitated by the intravenous administration of meperidine. Most clinical reports have attributed death in patients with asthma given narcotics to bronchoconstriction but investigations have not always shown this to be fact. Higgins and Means[108] did find a reduction in dead space which probably represented bronchoconstriction. Mitchell and DeJong[166] and Mitchell and Cooke[165] have investigated excised human and canine bronchial rings and observed that morphine did not produce bronchial constriction unless acetylcholine was added. Nalorphine had the

same effect as morphine, whereas codeine, dihydromorphinone, and meperidine did not. Similar results have been found in excised animal or human tracheal tissue by Adriani and Rovenstine[2] and by Fink and Akiyama.[76] As mentioned earlier, Shemano, Wendel, and Katinsky[212] have recently demonstrated that morphine and meperidine do not differ in their ability to produce bronchoconstriction in the dog.

Doubts have been expressed that bronchoconstriction is the cause of aggravation of respiratory distress after narcotics in asthmatic patients. Henriksen[105] reported that 15 of 702 asthmatic patients admitted to a Danish hospital died shortly after admission. Ten of the 15 had received morphine or similar narcotic within several hours prior to hospitalization. The clinical picture was that of respiratory failure without evidence of severe status asthmaticus. Postmortem findings revealed the bronchi to be almost totally occluded by sticky secretions. Thickening of secretions together with a depressed will or ability to cough could lead to a reduction in alveolar ventilation. Such a mechanism was postulated as being responsible for 3 cases of "morphine poisoning after therapeutic doses of morphine" in patients with bronchial asthma. One of the patients died.[113] These clinical and pathologic findings confirm those of Hibma and Curreri,[107] made in a patient with bronchopleurocutaneous fistula, that mixtures of morphine and belladonna drugs prolonged the appearance of dye in the sputum by nearly 100 per cent. Narcotics seem to possess a "drying" effect independent of the belladonna derivative. It would appear, therefore, that combination of a narcotic and a belladonna drug under these circumstances might augment "drying" and make the secretions doubly hard to move. However, Weinberg and Sensiba[250] have reported the use of 5 mg. methadone (or 50 mg. meperidine) with 0.4 mg. scopolamine intravenously as an emergency treatment for status asthmaticus in 100 patients without adverse response.

Wells[252] measured the airway resistance of patients with bronchial asthma and found that the mean airway resistance was markedly elevated—in some cases almost 25 times normal, presumably due to constricted air passages and retained secretions. Inspiratory resistance was found to be almost as high as expiratory resistance. He concluded that therapeutic measures must be directed toward lowering this resistance to air flow. Any measure that diminishes respiratory drive without decreasing the resistance to air flow predisposes to respiratory failure. Since narcotics would lower an elevated respiratry rate, diminish effective alveolar ventilation, reduce dead space which must represent bronchoconstriction, and depress the sensitivity of the respiratory center to the carbon dioxide stimulus, the possibilities of precipitating further trouble are great.[150] When a narcotic has been indicated in bronchial asthma, meperidine or similar drug seems to have been preferred clinically because of an assumed lessened predisposition to smooth muscle constriction. However, meperidine has been shown to produce bronchial constriction in the dog and, as will be discussed, it also is a potent liberator of another constrictor substance, histamine, as judged from cutaneous injection in man. Therefore the possibilities of further respiratory embarrassment after meperidine should not be overlooked. Perhaps this accounts for the observations of McDermott and Papper[152] previously mentioned.

Narcotics are potentially dangerous in bronchial asthma but not just from bronchoconstriction. Apparently other actions of these drugs upon respiration may contribute to inadequacy or failure of breathing.

3. Chest deformities. Congenital or acquired deformities of the chest may likewise reduce the respiratory reserve and predispose to catastrophe after narcotics. Kyphoscoliosis has been considered a condition in which patients are hypersensitive to narcotics.[77,120,145] These patients cannot be considered hypersensitive in the strict sense of the word. Rather they are unable

to compensate for even slight additional respiratory depression. Bergofsky[16] has presented abundant data demonstrating the degree of cardiorespiratory failure in kyphoscoliosis. The narrow margin by which compensation is maintained is evident from the data. Depression of respiration, therefore, has great significance however produced. Fishman[79] finds little difference in alveolar hypoventilation whether it be caused by kyphoscoliosis, ankylosing spondylitis, or obesity. The responses to narcotics by patients with these syndromes should be the same. Katz and Chandler[126] and Fischer and Dolehide[78] agree that it is the effects of kyphoscoliosis upon alveolar ventilation that make patients with this disease intolerant of narcotics. Similar reasoning might be applied to the numerous reports concerning the hypersensitivity to narcotics of patients with cor pulmonale coincident with or independent of kyphoscoliosis.[46,120,196,200,218]

Cyanosis and dyspnea. The administration of narcotics to cyanotic or dyspneic patients must be considered carefully. Patients with certain diseases manifesting these symptoms may obtain relief by narcotics whereas in patients with other disease entities with the same symptoms, narcotics may lead to disaster. Although there is at least one report claiming an increased sensitivity to narcotics during hypoxia,[163] the data are unimpressive. If cyanosis is caused by pulmonary insufficiency, narcotics are contraindicated. But if the cyanosis is a product of congenital heart disease, there is evidence that narcotics may be indicated under certain circumstances. Taussig[232] believes that a child with cyanotic congenital heart disease tolerates 1.0 mg. per 5 kilograms of body weight of morphine well. She has observed that infants with paroxysmal dyspnea, unconscious and apparently near death because of oxygen want induced by crying or excitement, have regained consciousness, improved in color, and become ambulatory within ½ hour after receiving morphine. This Taussig attributes to the metabolic depressant effect of morphine. Specific data on this action are lacking.

One must also differentiate between the compensatory dyspnea of oxygen want and the purposeless dyspnea seen with certain cardiac disorders. Under the latter circumstances, pulmonary ventilation is adequate, oxygen levels within normal limits, and the Pco_2 below normal. Anesthetics such as trichloroethylene[55] or ethyl ether[103] produce comparable tachypnea with the agents driving respiration by direct or reflex effects. Under these circumstances during anesthesia or disease, small doses of narcotics may depress the respiratory center, thus raise the threshold to either the carbon dioxide or pH stimulus, and depress the reflexes that are driving respiration. Pulmonary ventilation then returns to a more normal pattern. Patients with cardiac dyspnea may be greatly benefited by narcotics for this reason.

B. COMBINATION WITH GENERAL ANESTHETICS. Narcotics administered to an anesthetized patient or to one recovering from a general anesthetic are likely to cause a different respiratory effect than if the same dose of drug were given to the same patient in a normal state. This observation was apparently first made by Nussbaum[171] in 1863, who noted that a dose of morphine given during chloroform anesthesia would allow completion of the operation without further administration of chloroform. The same dose of morphine several days later in the postoperative period produced only the usual narcotic effect. Similar observations were made by Bernard[17] in animals from which came the practice of administering narcotics prior to anesthesia. While these data primarily concern the effect of narcotics upon the central nervous system, they apply to respiration as well. Narcotic preanesthetic medication, followed by an anesthetic that is not strongly stimulant to respiration (e.g., cyclopropane or thiopental[102]) commonly leads to apnea. The significance of this observation is strengthened by data that show a smaller concentration of anesthetic is needed to obtain a given plane

of anesthesia if a narcotic has been given.[233] Others[34] have denied this to be true. Appreciable respiratory depression does not appear with cyclopropane without preanesthetic narcotic except as anesthesia deepens. On the other hand,[55,121] narcotic premedication prior to ethyl ether and trichloroethylene anesthesia is likely to result in a slower, more regular respiration than if the narcotic is omitted.

If a usual therapeutic dose of narcotic is administered intramuscularly or intravenously to anesthetized patients, serious respiratory depression or apnea will occur in a high proportion of cases.[24,121] Immediately before and during anesthesia the dose of narcotic should be reduced. Observations have also been made that therapeutic doses of narcotics given to patients who have reacted incompletely from general anesthesia will frequently lead to reanesthetization of the patient, marked respiratory depression, and hypotension.[52,61,198] The latter phenomenon has been classified as a hazard of the immediate postoperative period.[48] Comparable responses have been noted after narcotics have been given to patients under the influence of alcohol. Moller[167] calls attention to 7 deaths resulting from the simultaneous presence of alcohol and morphine or barbiturate. Neither drug alone should have caused death in his opinion. Moller[167] estimated that the blood concentration of alcohol at the time of the morphine injection was between 2.2 and 2.7 per cent and that 0.3 to 0.4 mg. per kilogram of morphine was lethal.

The reasons for such exaggerated responses are not readily apparent. The effect cannot be considered merely additive but more likely is synergistic. Eckenhoff and Helrich[59] have shown that the respiratory response to endogenously accumulated carbon dioxide is progressively diminished by the successive addition of narcotic, thiopental, and nitrous oxide and that this response is reversed by subsequent elimination of nitrous oxide. Under the influence of the triple combination, and in a light plane of anesthesia, the respiratory response to high concentrations of carbon dioxide was slight. The question is raised that possibly an inhalant anesthetic might alter cell permeability or cell response so that the effect of a given blood stream concentration of narcotic might be intensified. This is only one of the alternatives. Thiopental and nitrous oxide may also produce a condition comparable to the previously mentioned diminution in sensory input by spinal anesthesia and thiopental, thereby leading to an exaggerated respiratory depression by the narcotic.

C. COMBINATION WITH PHENOTHIAZINES. Early data suggested that respiratory depression from a narcotic might be prevented or abolished by combination of the narcotic with a phenothiazine derivative.[142,187] Subsequent work does not seem to have confirmed this claim and suggests that phenothiazine drugs either intensify respiratory depression from narcotics or do not affect breathing at all. Fraser and Isbell[86] gave 10 and 30 mg. of morphine alone or in combination with chlorpromazine, 25 mg. intramuscularly or 50 mg. orally, and found that the respiratory depression induced by morphine was not altered in any way by combining the drugs. Lambertsen, Wendel, and Longenhagen,[138] however, gave chlorpromazine (25 mg. per 70 kilograms) and meperidine (100 mg. per 70 kilograms) alone and in combination to 6 normal volunteers and observed respiration stimulated with carbon dioxide controlled at 46 mm. Hg alveolar Pco_2. They observed that the maximal respiratory depression from the combination did not occur for 1½ hours after injection (as compared to 1 hour with meperidine alone) but that at 3½ hours the depression was still close to its maximal value. At 3½ hours the effects of meperidine alone had declined to approximately half the maximal value. They observed further that the action of the combination was chiefly one upon respiratory rate with no additional depression of tidal volume. The authors thought the enhanced respiratory depression was not an effect of summation of drug

actions and have discussed the possible causes. The most attractive suggestion to the reviewers was that chlorpromazine led to a reduction in the rate of meperidine inactivation and thus to more intense and prolonged action. Egbert and associates,[69] however, were unable to detect an intensification by promethazine of the respiratory depressant effect of meperidine, either in a group of volunteers or in a blind clinical study.

D. MUSCULAR RELAXANTS. While there are no indications that narcotics act upon the neuromuscular junction, or that muscle relaxants definitely act centrally, there are data concerning the simultaneous effect of the two drugs upon respiration. Zaimis and Cannard* have obtained evidence in man that postanesthetic apnea following the use of the two drugs may be more often due to the narcotic than was previously appreciated. Such distinction was made by demonstrating that after light thiopental and nitrous oxide anesthesia with sufficient succinylcholine to produce apnea, respiratory exchange had always returned by the time the neuromuscular junction responded to a nerve stimulus. However, if a narcotic had also been given as part of the anesthetic, respiratory exchange did *not* return until after the neuromuscular junction was functioning properly. This suggests that a narcotic antagonist may be of use in combating postanesthetic apnea or respiratory depression when narcotics as well as relaxants have been used and the apnea has failed to respond to a muscle relaxant antagonist.

These observations, while d[illegible] and quantitative, are neither unexpected nor surprising. The technique of so-called "controllable apnea" utilizing narcotics and muscle relaxants[36,81,82] is the clinical adaptation of this idea. In this technique, the action of each agent is specifically counteracted by an antagonist. Those who would advocate this technique,[145] however, should also point out that although specific antagonists exist for the narcotics, they are not always reliable and the antagonists for relaxants are not effective in counteracting the myoneural blocking effect of all clinically available relaxants.[177]

*Unpublished observations.

Circulation

The actions of narcotics upon the cardiovascular system have received less attention than have the effects upon respiration. In 1933, Schmidt and Livingston[206] wrote: "It is somewhat surprising to find very little satisfactory information in the literature upon the subject of the circulatory actions of a drug that is as widely used as morphine. These actions are usually regarded as unimportant, yet there is abundant evidence to indicate that morphine is a powerful depressor agent if it is injected intravenously." Kreuger, Eddy, and Sumwalt[136] observed in 1941 that "changes in heart rate and blood pressure beyond what would be expected to accompany the narcosis . . . [were] noted so frequently in animals and man that eventually a large number of investigations have been carried out to ascertain the degree and mechanism of such effects."

The principal consequence of narcotic action upon the circulation is hypotension. This has been demonstrated as a complication following the use of morphine in man as well as in animals.[136] It appears less appreciated, however, that this is a common effect of *all* narcotics. Hypotension following meperidine is often ignored or denied, yet, from the earliest use of this synthetic, alarming hypotension after intravenous or intramuscular injection was reported.[12,18,20,90,214] A résumé of the clinical reports of hypotension from the various narcotics in obtainable elsewhere.[68]

Of more practical significance for present purposes would be a comparison of the incidence of hypotension produced by the various narcotics, since all share this potential. However, comparative data are lacking and few narcotics have been tested in a manner which allows comparison. As with the investigation of narcotics and respiration, studies of circulatory effects

have been in normal volunteers, in whom a minimal response has been found unless stress has been placed upon the circulation. Papper and Bradley[175] were unable to detect a change in blood pressure in 4 normal subjects lying supine and given 10 mg. of morphine intravenously. When Drew, Dripps, and Comroe[47] injected 10 to 30 mg. of morphine in 49 supine subjects and patients, no significant change in blood pressure was measurable. Likewise, Denton and Beecher,[45] studying the side effects from morphine and 3 methadone derivatives in two groups of 28 and 29 normal subjects lying supine, failed to see a significant change in blood pressure. King, Elder, and Dripps,[134] did not observe a statistically significant change in blood pressure in 26 subjects and patients given 100 to 150 mg. meperidine intravenously. McCall and Taylor[151] saw only a slight decline in mean arterial blood pressure when 24 to 32 mg. of morphine was injected subcutaneously in 7 normal parturients. Similar data were obtained in normal subjects by Moyer, Morris, and Pontius[169] after the injection of 60 mg. morphine. Wikler, Fraser, and Isbell,[257] recorded a slight increase in blood pressure in a group of postaddiction subjects given 5 to 15 mg. nalorphine intramuscularly.

Even in patients who are ill and yet who remain supine, decrease in blood pressure from narcotics is not frequent. Starr and his associates[219] gave 10 or 15 mg. morphine subcutaneously to 7 patients who had heart disease but were not seriously ill. The average circulatory changes were not statistically significant. They also gave 15 to 30 mg. morphine to 8 patients with severe cardiac disease although none had congestive failure. Again changes in blood pressure were not significant.

To date the most commonly employed stress in the study of narcotic action upon the circulation has been use of the force of gravity by standardized "tilt table" tests. Such tests have been used clinically to test the adequacy of the circulation[6] as well as an investigational method. The first attempt to study the relationship of the position of the body to the competence of the circulation was apparently that by Hill[109] in 1895. His experiments in dogs were initiated by clinical observations that severe hypotension in erect patients could be relieved when they were placed recumbent. Weiss, Wilkins, and Haynes[251] introduced body tilt as a method of studying the effect of sodium nitrite upon the circulation and subsequently showed[258] that the hypotension produced by the nitrite occurred as a result of pooling of blood in the peripheral vascular bed with consequent cerebral anemia. When Batterman[11] and Prescott[183] examined the syncope that followed injection of meperidine in upright patients, they noted the similarity of the response to that reported to follow the injection of sodium nitrite.

Drew, Dripps, and Comroe[47] were the first to use the tilt test as a means for studying in man the effect of narcotics upon the circulation. When they injected 12 to 30 mg. morphine intramuscularly in 25 subjects and tilted them 75 degrees to the head-up position, 44 per cent fainted or showed signs of imminent circulatory collapse as compared to 8 per cent who demonstrated the same response prior to the morphine. When the 11 "fainters" had their legs bandaged and were tilted again, only those 2 who had fainted on the control tilt did so again. Marked hypotension occurred in each of the fainters. The authors concluded that morphine led to peripheral vascular dilatation and pooling of blood with resultant cerebral anemia. They warned against the use of morphine in patients in shock or those who were to assume an upright position.

King, Elder, and Dripps[134] used the same method in studying the effect of 100 and 150 mg. meperidine intravenously in 26 normal subjects or hospital patients. They observed only 6 instances of fainting or hypotension after meperidine as compared with 2 such reactions during the control tilt. Studies employing the same technique with minor variations have been re-

ported for nalorphine,[57] for dihydrocodeine,[64] for anileridine,[32,52] and for alphaprodine and combinations of alphaprodine or meperidine and levallorphan.[213] All these studies except the one for alphaprodine[213] have shown that hypotension after tilt is more common after the injection of narcotics than before. It is of interest that levallorphan did not counteract the circulatory effects produced by meperidine.[213]

While, superficially, data from the tilt-table tests may look convincing, their interpretation is not easy. Many factors can influence the results of this test, including: environmental temperature, apprehension, the state of digestion, lack of sleep, fear of vomiting and "making a spectacle of one's self," previous experience with the test, and pain at the site of arterial puncture for intra-arterial manometry. The interpretation of nausea and vomiting with the tilt is also not clear. Although assumption of the upright position increases the incidence of vomiting,[37] this may be precipitated by hypotension, but it may appear independently of hypotension. The action of other drugs given the patient before or during the studies may also affect results. As was noted in the section on respiration, studies of narcotic action are sometimes performed on patients given the narcotic for preanesthetic medication. It is appropriate to point out that atropine predisposes to hypotension after tilt.[125,164]

Severe hypotension, fainting, or vomiting would appear to be a rather extreme end point to have to obtain to investigate any drug even though such a test duplicates in patients conditions imposed by standing, sitting, steeply reclining, or other sudden changes in body position. These same reactions remove the test from among those that can be used with ease clinically. Also the mechanism of hypotension following change in body position[201] is not clear. A method that would be less hazardous, associated with less subjective symptoms, and be less time consuming would be profitable. Perhaps the Valsalva maneuver would serve this purpose.[118] Comparative data are needed.

Hypotension after narcotics can be produced by one or more cardiovascular actions. These include: (1) peripheral vascular dilatation, (2) direct depression of the vasomotor center, and (3) direct myocardial depression. These possibilities will be considered separately.

1. Vasodilatation. Schmidt and Livingston[206] concluded from their observations of the effect of morphine upon the dog's circulation that the primary factor responsible for hypotension was a dilatation of cutaneous and muscular blood vessels by a direct action of the narcotic upon their walls. Other narcotics appear to act in similar manner.[114] The evidence accumulated from man does not appear to contradict this conclusion. Drew, Dripps, and Comroe[47] showed that hypotension after tilt could be prevented by bandaging the subject's legs. They thought this minimized peripheral vascular pooling of blood and maintained a more effective circulating blood volume, thus preventing cerebral anemia. While there are no contradictory data, there appear few other confirmatory data of a direct vasodilator action in man. One could obtain indirect evidence from temperature recordings, but these too are lacking. With peripheral vasodilatation, skin temperature should rise and body temperature should decrease. No recording of skin temperature can be found but body temperature does decline.[136] The reduction is not great, however, and could be due to decreased bodily activity and diminished metabolic rate. Further measurements of this parameter are required. Data might also be obtained by plethysmography or by measuring muscle blood flow with radioactive substances.

If one accepts peripheral vasodilatation and pooling of blood as the mechanism for hypotension following narcotics, then a method for treating such hypotension is readily apparent. If postural hypotension can be treated by assumption of the recumbent position, hypotension occurring after narcotics in the recumbent position should

be amenable to treatment by raising the legs. This would return blood to the effective circulation and raise the blood pressure. Peterson, Eather, and Dripps[179] have shown this to be worth while in treating shock under some circumstances.

Histamine liberation. Several clinicians have noted histamine responses in patients who have had sudden severe hypotension and collapse following narcotics.[27,262] While such reactions may suggest a relationship between narcotics and histamine release, they do not prove it. The reviewers have many times noted wheals along veins into which narcotics have been injected without detectable change in blood pressure. Narcotics do have the ability to cause the release of histamine[74,195]; the amount released is dependent upon the dose of narcotic, and the incidence of such release is not the same for all narcotics.[52,74] Feldberg and Paton[74] noted the absence of, or slow recovery from, hypotension after narcotics was different from that noted after other histamine liberators. They also observed that less histamine was detectable after morphine-induced hypotension than would be found after hypotension induced with other histamine liberators. They considered this evidence for other depressor action of narcotics. Schacter[203] has remarked upon the similarity between meperidine, atropine, and quinine in so far as their potential for releasing histamine is concerned. Finer and Partington[75] observed the "triple response" in patients given subcutaneous and intravenous meperidine and thought it less likely to appear with subsequent injections for the next 24 hours after it had been produced once. They also noted that prior administration of antihistaminics blocked the response. Gershon and Shaw[89] presented data from dogs to suggest that the initial hypotensive response to a narcotic might be related to a simultaneous release of histamine. If this were not liberated at the time of injection but was released later, hypotension did not appear and in fact an elevation in blood pressure was sometimes seen. This would agree with earlier observations by Feldberg and Paton[74] in cats that the release of histamine following narcotics is "an explosive" one if hypotension occurs. Christie and associates[33] noted, "In cases of morphine overdosage in man there is often an accompanying fall in blood pressure. Therefore it is interesting to note that when cyclizine was given intravenously to our patients after the administration of large doses of morphine (up to 100 mg.), there was a rise in blood pressure in every case." One of the most interesting observations has been that of Van Arman and Sturtevant[240] who noted that meperidine injected intravenously in dogs anesthetized with pentobarbital produced a steep fall in blood pressure within 20 seconds. Blood samples taken at the lowest point of fall were found by guinea pig test to contain large amounts of histamine. When blood pressure had returned to normal, histamine could not be found in samples withdrawn at that time. Diphenhydramine* blocked the appearance of hypotension even though histamine could be demonstrated to be present. The dogs developed a tolerance to the pressure-lowering effects of repeated doses of meperidine, probably as a result of the depletion of histamine stores. These latter observations confirm those of Schmidt and Livingston,[206] who injected morphine rather than mepridine. In evaluation of data, however, we must keep in mind species' difference in tissue susceptibility to histamine liberators.[74]

From the foregoing two paragraphs one can conclude that hypotension following narcotics is at least in part associated with the liberation of histamine which leads to dilation of peripheral blood vessels and pooling of blood.

2. Direct depression of the vasomotor center. Evans, Nasmyth, and Stewart,[70] studying the hypotension produced by 4 mg. per kilogram of morphine, injected intravenously in cats, observed that the hypotension was only partially caused by his-

*Benadryl.

tamine release and was not completely blocked by antihistaminics. A central effect appeared to them to participate in producing hypotension, but precise definition of that central effect has been lacking. Feldberg and Paton[74] arrived at a similar conclusion, and their reasons were presented above. Stross[136] also suggested that morphine acted through the vasomotor center, the appearance of a depressor effect on this basis being masked by the stimulant actions of accumulated carbon dioxide. There has been no confirmation of this suggestion but in view of the recent demonstration of the ability of carbon dioxide to stimulate the sympathoadrenal mechanisms,[234] it might be worth re-examining. Wikler,[255] in reviewing the effects of morphine and related drugs upon the nervous system, could not find support for the idea that narcotics exerted a significant effect upon the vasomotor center.

The action of narcotics upon the cardiac pressor reflexes, as from the carotid sinus, is likewise not agreed upon by all investigators.[136] Although there have been claims that these reflexes are enhanced by narcotics,[197] there appears to be no confirmatory evidence.

3. Direct myocardial depression. Schmidt and Livingston[206] concluded from their extensive examination of the actions of morphine upon the circulation of animals that whereas morphine would depress the isolated heart, indicating a direct myocardial effect, the heart in situ was not affected by doses sufficient to cause marked fall in blood pressure. There are no observations in man to dispute this conclusion. Newer data from animals which suggest myocardial depression by narcotics include the following: A similarity between meperidine and a group of drugs consisting of atropine, quinidine, procaine, and certain of the antihistaminics has been noted.[26] Quinidine and procaine directly depress myocardial muscle. One might assume that because of other similarities meperidine could also have this potential. Sugioka, Boniface, and Davis[224] were able to demonstrate that 5 mg. per kilogram of meperidine in the intact dog anesthetized with pentobarbital produced a transient depression in myocardial contractility, an elevation of cardiac rate, and persistent hypotension. Larger doses produced severe hypotension progressing to death. Calesnick, Smith, and Beutner[28] demonstrated a synergism in rats between quinidine, meperidine, and procaine, and concluded that mixtures of these drugs were cardiotoxic. Their investigation was prompted by alarming reactions observed in patients who had been given this combination. Huggins, Seibert, and Bryan[116] believed that morphinized dogs require less potassium by infusion to cause a disappearance of P waves than do dogs under the influence of barbital. This has suggested to them that morphine increases the susceptibility of the heart to potassium ions.

In addition to predisposing to hypotension, narcotics may alter heart rate and cardiac output.

Heart rate. Animals, and particularly dogs, develop bradycardia after the injection of morphine.[136] Such an effect has not been observed uniformly in man,[180] however. Papper and Bradley[175] considered the change in heart rate insignificant in 6 normal subjects lying supine and given 10 mg. morphine intravenously. Denton and Beecher[45] saw statistically significant slowing of the pulse rate (7 beats per minute) in 29 subjects given morphine or three methadone derivatives. Wikler, Fraser, and Isbell[257] also noted a slight slowing of cardiac rate after the injection of 5 to 15 mg. nalorphine in postaddict volunteers. Drew, Dripps, and Comroe,[47] however, observed an average increase of 19 beats per minute in 19 supine subjects and patients given 10 to 30 mg. morphine intravenously, but when these doses were given intramuscularly to 30 patients there was no statistically significant change. One can conclude that morphine does not appreciably alter cardiac rate in man lying supine.

Meperidine does not appear to act in similar fashion. There are numerous observations indicating an occasional striking and even alarming rise in pulse rate after meperidine. Johnstone[121] gave 50 mg. meperidine, intravenously, to 15 normal patients and noted, "slight increases—three or four beats—in the sinus rates of a few of the patients, attributable to emotional factors; the sinus rates of the remainder were unchanged." King, Elder, and Dripps[134] reported a statistically significant increase in pulse rate in 26 subjects given 100 to 150 mg. meperidine intravenously. Harvey, Berkman, and Leonard[101] have presented the case records of 5 patients with auricular flutter in whom meperidine, 75 and 100 mg., intramuscularly, produced an alarming increase in heart rate. Two other case records from patients with the same symptom complex treated similarly failed to display tachycardia. The authors caution against the use of this agent in patients with heart disease. Eckenhoff and Helrich,[60] in a blind study of preanesthetic medication, observed that narcotics (morphine, meperidine, and alphaprodine) led to a statistically significant increase in pulse rate more often than did a placebo or secobarbital. This increase was most notable with meperidine; 45 per cent of the patients given this drug for medication responded with a rise in pulse rate. It was necessary to cancel operation in one patient with persistent tachycardia. There are no data to suggest that other drugs of the same chemical group (alphaprodine and anileridine) have the same potential.[32,52]

The mechanisms by which these changes in heart rate are produced are not clear. In animals morphine leads to a slowing in part as a result of a stimulation of vagal centers and possibly by other central effects as well.[136] Breckenridge and Hoff[21] thought that the bradycardia might be due to a selective depression of the supramedullary centers suppressing autonomic reflexes. While one would expect the sedation seen after narcotics to slow heart rate, it is difficult to know how important this is. Jones, Price, Linde, and Dripps[122] did not observe slowing of the heart rate until after patients, premedicated with morphine, were anesthetized with cyclopropane. Those patients not given morphine prior to anesthesia did not develop slower rates. Johnstone[121] likewise called attention to the effect of the combination of cyclopropane and narcotic. He gave 100 mg. meperidine to 15 patients and then anesthetized them with cyclopropane. Sinoauricular nodal bradycardia was seen in 12 of the patients and atrioventricular nodal bradycardia in the other 3. The intravenous injection of atropine, 0.65 mg., was followed within 30 seconds by the appearance of sinus tachycardia in every patient.

These observations suggest that narcotics may increase vagal tone in normal persons, but that this is masked in an unknown manner. It is revealed only when the patient is anesthetized with a substance such as cyclopropane. This response would agree with other data[181] that refute the claim that meperidine produces atropine-like or parasympatholytic effects.[101,203] If there were an atropine effect, one might expect tachycardia as does frequently appear, but one would not expect a slowing after cyclopropane as seen with morphine. Also more of a vagolytic effect could theoretically appear if meperidine was combined with atropine although there are no data on this. The data previously quoted from Eckenhoff and Helrich[60] were in patients who did have atropine, but those from Harvey, Berkman, and Leonard[101] did not.

Reduction in cardiac output. Starr and associates[219] observed minimal changes in cardiac output (ballistocardiograph) in 7 patients with heart disease given 10 to 15 mg. morphine subcutaneously. In 8 other patients with severe cardiac disease given 15 to 30 mg. morphine by the same route, cardiac output diminished but not strikingly so. Papper and Bradley[175] noted no change in cardiac output, also by ballistocardiograph, in 4 normal subjects given 10 mg. morphine intravenously and a rise in

2 other subjects, given the same dose of drug. Drew, Dripps, and Comroe[47] recorded an increase in cardiac output, again by ballistocardiograph, in 6 of 7 normal subjects given 15 mg. morphine intravenously. They thought the increase was due to the elevation in heart rate because there was no change in stroke volume. Malt[154] was unable to detect a change in the ballistocardiogram in normal supine volunteers given 10 mg. morphine.

It appears again that in the normal patient, as well as the one with some forms of cardiac disease, there is no significant alteration of cardiac output following the injection of morphine. Meperidine does not appear to have been studied in this regard.

The action of narcotics on organ blood flow. There is scant evidence of an appreciable effect of narcotics upon the blood flow of any organ with the possible exception of the kidney, so long as the hypotensive propensity of the drugs is taken into account.

McCall and Taylor[151] gave 24 to 32 mg. morphine subcutaneously to 19 pregnant women, 7 of whom were having a normal pregnancy and 12 of whom had preeclampsia. Cerebral blood flow was measured by the nitrous oxide method before and after the morphine. In both groups morphine led to a slight reduction in mean arterial blood pressure, a slight rise in cerebral blood flow, a corresponding slight increase in cerebral oxygen uptake, and a slight diminution in vascular resistance. None of these changes were considered statistically significant. Keats and Mithoeffer[129] propose that the elevation in cerebral blood flow is a result of the increased arterial Pco_2 after morphine and that this leads to the rise in cerebrospinal fluid pressure commonly observed after morphine. Hyperventilation, with its consequent hypocapnia and cerebrovascular constriction, causes cerebrospinal fluid pressure to diminish. Nalorphine, by reversing respiratory depression from narcotics, would be expected to cause a similar decline in Pco_2 and likewise to cause cerebrospinal fluid pressure to fall. Keats and Mithoeffer[129] observed this to be true. Moyer, Morris, and Pontius[169] gave 60 mg. morphine to normal subjects and also noted a slight but statistically insignificant increase in cerebral blood flow with a concomitant diminution in arterial oxygen and elevation in carbon dioxide levels. With this large dose of morphine, they recorded a 50 per cent decrease in cerebral oxygen uptake. All of these changes were reversed by the intravenous injection of 25 mg. nalorphine.

Sokoloff,[217] reviewing the action of drugs upon the cerebral circulation, concluded, "On the basis of present evidence, it appears that morphine and other similar narcotics have no significant direct action on the cerebral circulation but as a consequence of respiratory depression and carbon dioxide retention, which frequently attends their administration, cerebral blood vessels may be dilated and flow increased."

The effect of narcotics upon coronary blood flow of either man or intact animals does not appear to have been studied. Kreuger and associates[136] summarized the action of morphine on the perfused isolated heart and found that all experiments revealed coronary dilatation.

Habiff, Papper, Bradley, and associates[97] observed the effect on renal blood flow of 100 mg. meperidine in 8 subjects and 10 mg. morphine in 2 subjects. Effective renal plasma flow was decreased to a statistically significant degree from 24 to 50 per cent. These changes were interpreted as evidence of intrarenal vasoconstriction.

Smythe and Gilmore[216] studied the effect of morphine, 1 mg. per kilogram, upon hepatic blood flow measured by the Bromsulphalein method in dogs lightly anesthetized with pentobarbital. There was no statistically significant change in hepatic blood flow, hepatic arteriovenous oxygen difference, splanchnic oxygen consumption, or splanchnic vascular resistance. The avoidance of narcotics in patients with liver damage is presumably on the basis of their diminished ability to metabolize the drugs,[56] rather than of an influence of the

narcotics upon hepatic blood flow per se. Whatever influence they have upon hepatic flow is probably dependent upon other actions of the drugs such as vasodilatation and carbon dioxide accumulation.

The effect of narcotic antagonists on the circulation. Nalorphine and levallorphan produce essentially the same effects upon the circulation as do morphine and meperidine. Generally no striking change in blood pressure or pulse rate in patients or subjects lying supine and given from 5 to 25 mg. nalorphine intramuscularly or intravenously has been reported.[87,115,141,257] Eckenhoff, Elder, and King,[57] however, recorded observations from one volunteer given 10 mg. nalorphine intravenously, whose blood pressure declined from 125/75 to 75/40 mm. Hg within 15 minutes with the subject remaining in the supine position. This subject fainted when tilted to the 60 degree head-up position as did another of 3 subjects given 5 mg. nalorphine intravenously.

The hypotension produced by the injection of large doses of narcotics is effectively counteracted by nalorphine or levallorphan, although the effect comes on more slowly than does the respiratory antagonistic action.[1,54,57,58,62,65,139] Pretreatment with nalorphine or levallorphan does not appear necessarily to block hypotension from subsequently injected narcotics,*[213] even though the respiratory depressant effect of the narcotic was proved to be blocked.

Factors tending to increase hypotension

The action of narcotics upon the circulation is intensified under conditions similar to those augmenting the effect of narcotics upon respiration.

Shock and circulatory stress. Narcotics given in the presence of circulatory stress, especially if that stress is associated with a lowered blood volume, are apt to produce a higher incidence of hypotension than usual. During hemorrhage or in shock, blood pressure can be lowered further and resuscitation made more difficult because of the vasodepressor effect of the drugs.[50,143] Minimal doses of narcotics have been advised for pain relief under these circumstances. However, Stone, Mackrell, Brandstater, Haidak, and Nemir[222] have made some interesting observations on the use of morphine in the relief of cerebral distress and hyperpnea accompanying hemorrhagic shock. Normal volunteers were bled 20 to 38 per cent of their estimated blood volume with a resultant reduction in mean arterial blood pressure of 48 to 59 per cent. In one subject under these circumstances, arterial Pco_2 decreased from 36 to 19 mm. Hg, cerebral vascular resistance decreased from 2.3 to 1.5 mm. Hg per milliliter per 100 grams brain per minute, and cerebral blood flow 44 to 36 ml. per 100 grams brain per minute. After these measurements were made, 10 mg. of morphine was injected intravenously. The arterial Pco_2 rose to 25 mm. Hg, cerebral vascular resistance declined further to 1.2 mm. Hg, and cerebral blood flow increased to 45 ml. These changes were associated with marked subjective improvement and a relief of hyperpnea. It should be apparent, however, that, under these circumstances, a narcotic would be a "double-edged sword." While relieving subjective discomfort and hyperpnea and improving cerebral blood flow, it also may predispose to further hypotension through peripheral vasodilation.

Despite the above, the narcotics have been and remain one of the best therapeutic agents available for certain types of circulatory disease. Under what conditions may narcotics be helpful and by what mechanism? In those circulatory diseases where mild peripheral vasodilation is helpful, the narcotics are probably beneficial. A desirable fall in venous pressure has been measured following the use of morphine in patients with cardiac disease associated with high venous pressure.[73,91,202] If, however, this effect is counterbalanced by respiratory depression, lowered arterial oxy-

*Gans, J. H.: Unpublished observations.

gen content, and elevated arterial carbon dioxide content, then the result would not be desirable. The appearance of unwanted side effects may not be the result so much of the use of the narcotic as rather of the failure of the physician to appreciate the patient's individual problem or of his having erroneously guessed the dose.[246] Starr and associates[219] were unable to demonstrate significant effects of morphine on the circulation in patients with severe heart disease. Yet they concluded, "That morphine benefits patients seriously ill with cardiac disease is unquestioned. The usual explanation is that the drug, by quieting the patient, reduces the metabolic rate and so permits a slower circulation maintained by reduced cardiac effort. We regard our results as giving slight support of this conception. The diminution of cardiac work after morphine is somewhat more obvious in our cardiac cases, though absent in the more normal persons. In still more restless patients a greater reduction in both metabolic rate and cardiac work would be expected." The value of sedation, pain relief, and diminished body metabolism afforded by narcotics in the presence of circulatory diseases not associated with oxygen want or carbon dioxide retention must be considerable.

Anesthetics. Greisheimer, Ellis, Makarenko, and Stewart[92,93] and Murano and Tanaka[170] have shown in animals that cardiac output, blood pressure, and heart rate are consistently lower if morphine is given prior to administration of anesthetic agents. Murano and Tanaka postulated that the greater reduction in blood pressure seen after morphine in anesthetized dogs is due to the abolition by the general anesthetic of unspecified central compensatory influences. Jones, Price, Linde, and Dripps[122] have observed that the increase in cardiac output normally produced by cyclopropane in man is prevented by the preanesthetic administration of morphine. They conclude, "We view disease, trauma, and narcotics . . . as forces which draw out and attenuate the defense reserves of the body, leaving it more poorly equipped to deal with additional hazard."

Upon occasion, narcotics may have a beneficial effect upon heart rate and rhythm in the anesthetized patient. Johnstone[121] injected 25 mg. meperidine intravenously in 25 patients anesthetized with trichloroethylene and demonstrating multifocal ventricular arrhythmia or bigeminal rhythm. The arrhythmia disappeared within 4 minutes after the meperidine was given provided respiration was maintained or assisted adequately. Johnstone postulated that bronchiolar dilatation facilitated the removal of carbon dioxide and this was indirectly responsible for the observed change. Since bronchiolar dilatation after meperidine appears unlikely, perhaps the better explanation is improved control of respiration afforded by the narcotic, thus enabling better pulmonary ventilation. With the use of more potent anesthetics, the same effect might be obtained by deepening the level of anesthesia.

Phenothiazines. The combination of narcotic with a phenothiazine derivative theoretically carries a greater threat to the circulation than it does to the respiration. The phenothiazines are potent vasodepressors,[53,63] particularly predisposing to postural hypotension. Since the narcotics act in similar, although milder, fashion, one might predict that hypotension would appear more commonly than with either drug alone. Data are lacking, however. In view of the common intravenous use of these combinations in obstetrics, a study of the circulatory effects should be made. In the reviewers' experience, appreciable hypotension may follow the movement of parturients from bed to delivery table after having been given meperidine and phenothiazines simultaneously.

Appraisal

After the available data have been reviewed, conclusion is inescapable that, although narcotics are depressant to respiration and to circulation, in neither instance is the mechanism of the depression more

than vaguely understood. In normal man, the effect of the drugs upon these two body systems may be so slight as to escape detection in the absence of tests specifically designed to amplify the depressant action. Even here, it is not certain what the tests are evaluating.

The critically or chronically ill and the anesthetized are less tolerant of narcotics. While this is often evident to the clinician, it has not been quantitated. Why should the reaction to narcotics be related to the state of health or of consciousness? Probably this question is closely linked to the mechanism of action of narcotics, and likely anesthetics as well, since there is little reason to believe there is any essential difference in narcotics and anesthetics in this respect, except in the degree of effect produced. Anesthetics in dilute concentration can provide analgesia without loss of consciousness and narcotics can be given in sufficient amounts to allow surgical operation to be performed.

Failure to attack many of the fundamental problems related to the action of the narcotics can be attributed to two factors: dilution of effort and improper design of clinical experiments. There are a large number of narcotics for clinical use, but, unfortunately, nowhere is there available unbiased comparative data on their analgesic effectiveness and side reactions. There is not even convincing evidence that any of the synthetic substances surpass morphine. These narcotics have appeared because of a search for better and safer analgesics and because of the desire of each pharmaceutical company to have its own product. Both reasons are valid, yet if fewer narcotics had been produced investigation of pharmacologic effects and mechanisms of actions might have been more thorough.

In the last 20 years, increasing emphasis has been placed upon investigation of drug action in man rather than in animals. The clinician, untrained in research, has become involved in the study of new drugs among which have been the narcotics. The pharmaceutical industry must have its compounds evaluated in man to obtain Food and Drug Administration approval and for product support. Often these companies have not sought competent investigators or have been unable to interest those in the best position to do clinical research. Recourse has then been had to physicians unequal to the task.

Clinical investigation can be nearly as rigidly controlled as laboratory research. Studies must be carefully planned, the results analyzed by accepted techniques and thoughtfully compared to available standards. Pharmaceutical firms should be unwilling to support other than such studies. When this type of evaluation is combined with that which can come from industry's pharmacologic laboratories, advances in knowledge should result.

References

1. Adriani, J., and Kerr, M.: Clinical Experiences in the Use of N-allylnormorphine (Nalline) as an Antagonist to Morphine and Other Narcotics in Surgical Patients, Surgery 33:731-736, 1953.
2. Adriani, J., and Rovenstine, E. A.: The Effect of Anesthetic Drugs Upon Bronchi and Bronchioles of Excised Lung Tissue, Anesthesiology 4:253-262, 1943.
3. Alexander, J. K., West, J. R., Wood, J. R., and Richards, D. W.: Analysis of the Respiratory Response to Carbon Dioxide Inhalation in Varying Clinical States of Hypercapnia, Anoxia and Acid Base Derangement, J. Clin. Invest. 34:511-532, 1955.
4. Anscombe, A. R.: Pulmonary Complications of Abdominal Surgery, London, 1957, Lloyd-Luke.
5. Anscombe, A. R., and Buxton, R. St. J.: Effect of Abdominal Operation on Total Lung Capacity and Its Subdivision, Brit. M. J. 2:84-87, 1958.
6. Artz, C.: Evaluation of a Standard Tilt Test for Estimation of Blood Volume Deficiency, S. Forum 5:803-808, 1954.
7. Auerbach, J., and Coakley, C. S.: The Effect of Nisentil (Alphaprodine HCl) and Lorfan (Levallorphan) Tartrate on Respiration, Anesth. & Analg. 35:460-467, 1956.
8. Axelrod, J.: The Enzymatic N-demethylation of Narcotic Drugs, J. Pharmacol. & Exper. Therap. 117:322-330, 1956.

9. Axelrod, J., and Cochin, J.: The Inhibitory Action of Nalorphine on the Enzymatic N-demethylation of Narcotic Drugs, J. Pharmacol. & Exper. Therap. **121**:107-112, 1957.
10. Baker, F. J.: Pethidine and Nalorphine in Labour, Anaesthesia **12**:282-292, 1957.
11. Batterman, R. C.: Clinical Effectiveness and Safety of a New Synthetic Analgesic Drug, Demerol, Arch. Int. Med. **71**:345-356, 1943.
12. Batterman, R. C., and Himmelsbach, C. K.: Demerol—a New Synthetic Analgesic, J.A.M.A. **122**:222-226, 1943.
13. Becker, H. M., Nassr, H., and Schwab, M.: Vergleichende Untersuchungen über den Einfluss von Theophyllin-Äthylendiamin (Euphyllin), Oxyäthyl-Theophyllin (Cordalin), Coramin, N-Allylnormorphin und Levallorphan auf die durch Morphin und Dromoran gehemmte Atmung, Klin. Wchnschr. **34**:891-895, 1956.
14. Bellville, J. W., Howland, W. S., Seed, J. C., and Houde, R. W.: The Effect of Sleep on the Respiratory Response to Carbon Dioxide, Anesthesiology **20**:628-634, 1959.
15. Bellville, J. W., Wallenstein, S. L., Wald, G. H., Dowling, M. D., and Houde, R. W.: Effect of Noscapine and Codeine on the Respiratory Response to Carbon Dioxide, Anesthesiology **19**:545-551, 1958.
16. Bergofsky, E. H., Turino, G. M., and Fishman, A. P.: Cardiorespiratory Failure in Kyphoscoliosis, Medicine **38**:263-317, 1959.
17. Bernard, C.: Leçons sur les anesthésiques et sur l'asphyxie, Paris, 1875, Baillière et Fils.
18. Bieter, R. N., and Hirsh, S. A.: Methadone in Internal Medicine, Ann. New York Acad. Sc. **51**:137-144, 1948.
19. Bodman, R. I.: The Depression of Respiration by the Opiates and Its Antagonism by Nalorphine, Proc. Roy. Soc. Med. **46**:923-930, 1953.
20. Branwood, A. W.: Clinical Trials of Pethidine, Edinburgh M. J. **50**:177-182, 1943.
21. Breckenridge, C. G., and Hoff, H. E.: Influence of Morphine on Respiratory Patterns, J. Neurophysiol. **15**:57-74, 1952.
22. Breckenridge, C. G., and Hoff, H. E.: Pharmacological Analysis of the Nervous Control of Respiration by d-l-Dromoran, Arch. internat. pharmacodyn. **93**:1-32, 1953.
23. Bromage, P. R.: Spirometry in Assessment of Analgesia After Abdominal Surgery, Brit. M. J. **2**:589-591, 1955.
24. Brotman, M., and Cullen, S. C.: Supplementation With Demerol During Nitrous Oxide Anesthesia, Anesthesiology **10**:696-705, 1949.
25. Bullough, J.: Use of Premixed Pethidine and Antagonists in Obstetrical Analgesia, Brit. M. J. **2**:859-862, 1959.
26. Burn, J. H.: Pharmacological Action of Antihistamine Compounds, Brit. M. J. **2**:691-693, 1950.
27. Butler, E. B.: A Case of Hypersensitivity to Pethidine in a Woman in Labour, Brit. M. J. **2**:715-716, 1951.
28. Calesnick, B., Smith, N. H., and Beutner, R.: Combined Action of Cardiotoxic Drugs: A Study on the Acute Toxicity of Combined Quinidine, Meperidine, Pentobarbital, Procaine, and Procaine Amide, J. Pharmacol. & Exper. Therap. **102**:138-143, 1951.
29. Cappe, B. E., Himel, S. Z., and Grossman, F.: The Use of a Mixture of Morphine and N-allylnormorphine as an Analgesic, Am. J. Obst. & Gynec. **66**:1231-1234, 1953.
30. Cappe, B. E., and Pallin, I. M.: Recent Advances in Obstetric Analgesia, J.A.M.A. **154**:377-379, 1954.
31. Chalmers, J. A., and Thornberry, C. J.: N-allylnormorphine (Lethidrone) in the Treatment of Neonatal Asphyxia, J. Obst. & Gynaec. Brit. Emp. **61**:244-247, 1954.
32. Chang, F. F., Safar, P., and Lasagna, L.: Narcotic Potency and Side Effects of Anileridine and Meperidine in Man, J. Pharmacol. & Exper. Therap. **123**:370-378, 1958.
33. Christie, G., Gershon, S., Gray, R., Shaw, F. H., McCance, I., and Bruce, D. W.: Treatment of Certain Side Effects of Morphine, Brit. M. J. **1**:675-680, 1958.
34. Cohen, E. N., and Beecher, H. K.: Narcotics in Preanesthetic Medication, J.A.M.A. **147**:1664-1668, 1951.
35. Cohen, S. J., and McGuigan, H.: The Effect of Morphine on the Respiratory Center, J. Pharmacol. & Exper. Therap. **23**:145, 1924.
36. Colemen, D. J., Hargrove, R. L., and Jones, P. O.: Controlled Respiration by Central Depression, Anaesthesia **13**:59-62, 1958.
37. Comroe, J. H., and Dripps, R. D.: Reactions to Morphine in Ambulatory and Bed Patients, Surg. Gynec. & Obst. **87**:221-224, 1948.
38. Cooper, D. Y., and Lambertsen, C. J.: Effect of Changes in Tidal Volume and Alveolar Carbon Dioxide Tension on Physiological Dead Space, Anesthesiology **18**:160, 1957.
39. Costa, P. J., and Bonnycastle, D. D.: The Effect of Levallorphan Tartrate, Nalorphine HCl, and Win 7681 (1-allyl-4-phenyl-4 carbethoxypiperidine) on Respiratory Depression and Analgesia Induced by Some Active Analgetics, J. Pharmacol. & Exper. Therap. **113**:310-318, 1955.
40. Cullen, S. C., and Santos, C. C.: Analgesia for Chronic Pain Without Respiratory Depression, A.M.A. Arch. Surg. **69**:410-414, 1954.
41. Cushney, A. R.: The Action of Drugs on the

Respiration, Proc. Roy. Soc. Med. **6**:123-130, 1913.

42. Cushney, A. R.: On the Pharmacology of the Respiratory Center, J. Pharmacol. & Exper. Therap. **4**:363-398, 1913.
43. Daly, R.: Morphine Hypersensitivity in Kyphoscoliosis, Brit. Heart. J. **7**:101-103, 1945.
44. Davis, J. S.: The Effect of Morphine on the Respiration in Pneumonia, J. Clin. Invest. **6**:187-202, 1929.
45. Denton, J. E., and Beecher, H. K.: New Analgesics. II. A Clinical Appraisal of the Narcotic Power of Methadone and Its Isomers, J.A.M.A. **141**:1146-1153, 1949.
46. Dönhardt, A., and Schernau, K.: Untersuchungen über die Aufhebung der Atemdepression durch Morphin und Morphinderivate, Anaesthesist. **6**:72-74, 1957.
47. Drew, J. H., Dripps, R. D., and Comroe, J. H.: Clinical Studies on Morphine. II. The Effect of Morphine Upon the Circulation of Man and Upon the Circulatory and Respiratory Responses to Tilting, Anesthesiology **7**:44-61, 1946.
48. Dripps, R. D.: Hazards of Immediate Postoperative Period, J.A.M.A. **165**:795-799, 1957.
49. Dripps, R. D., and Comroe, J. H.: Clinical Studies on Morphine. I. The Immediate Effect of Morphine Administered Intravenously and Intramuscularly Upon the Respiration of Normal Man, Anesthesiology **6**:462-468, 1945.
50. Dripps, R. D., and Comroe, J. H.: Circulatory Physiology: The Adjustment to Blood Loss and Postural Changes, S. Clin. North America **26**:1368-1376, 1946.
51. Dripps, R. D., and Dumke, P. R.: The Effect of Narcotics on the Balance Between Central and Chemoreceptor Control of Respiration, J. Pharmacol. & Exper. Therap. **77**:290-300, 1943.
52. Dripps, R. D., Millar, R. A., and Kneale, D. H.: A Comparison of Anileridine, Morphine, and Meperidine in Man, Surg. Gynec. & Obst. **105**:322-326, 1957.
53. Dripps, R. D., Vandam, L. D., Pierce, E. C., Oech, S. R., and Lurie, A. A.: The Use of Chlorpromazine in Anesthesia and Surgery, Ann. Surg. **142**:774-785, 1955.
54. Dulfano, M. J., Mack, F. X., and Segal, M. S.: Therapy of Respiratory Acidosis With N-allylnormorphine, New England J. Med. **248**:931-934, 1953.
55. Dundee, J. W., and Dripps, R. D.: Effects of Diethyl Ether, Trichloroethylene, and Trifluoroethylvinyl Ether on Respiration, Anesthesiology **18**:282-289, 1957.
56. Dundee, J. W., and Tinckler, L. F.: Pethidine and Liver Damage, Brit. M. J. **2**:703-704, 1952.
57. Eckenhoff, J. E., Elder, J. D., and King, B. D.: N-allylnormorphine in the Treatment of Morphine or Demerol Narcosis, Am. J. M. Sc. **223**:191-197, 1952.
58. Eckenhoff, J. E., and Funderburg, L. W.: Observations in the Use of the Opiate Antagonists Nalorphine and Levallorphan, Am. J. M. Sc. **228**:546-553, 1954.
59. Eckenhoff, J. E., and Helrich, M.: The Effect of Narcotics, Thiopental, and Nitrous Oxide Upon Respiration and the Respiratory Response to Hypercapnia, Anesthesiology **19**:240-253, 1958.
60. Eckenhoff, J. E., and Helrich, M.: Study of Narcotics and Sedatives for Use in Preanesthetic Medication, J.A.M.A. **167**:415-422, 1958.
61. Eckenhoff, J. E., Helrich, M., Hege, M. J. D., and Jones, R. E.: Respiratory Hazards of Opiates and Other Narcotic Analgesics, Surg. Gynec. & Obst. **101**:701-708, 1955.
62. Eckenhoff, J. E., Helrich, M., Hege, M. J. D., and Jones, R. E.: The Combination of Opiate Antagonists and Opiate for the Prevention of Respiratory Depression, J. Pharmacol. & Exper. Therap. **113**:332-340, 1955.
63. Eckenhoff, J. E., Helrich, M., and Rolph, W. D.: The Effects of Promethazine Upon Respiration and Circulation of Man, Anesthesiology **18**:703-710, 1957.
64. Eckenhoff, J. E., Helrich, M., and Rolph, W. D.: The Effect of Dihydrocodeine Upon Respiration and Circulation in Man, Anesthesiology **18**:891-896, 1957.
65. Eckenhoff, J. E., Hoffman, G. L., and Dripps, R. D.: N-allylnormorphine: An Antagonist to the Opiates, Anesthesiology **13**:242-251, 1952.
66. Eckenhoff, J. E., Hoffman, G. L., and Funderburg, L. W.: N-allylnormorphine: An Antagonist to Neonatal Narcosis Produced by Sedation of the Parturient, Am. J. Obst. & Gynec. **65**:1269-1275, 1953.
67. Eckenhoff, J. E., and Norton, M. L.: The Treatment of Intractable Pain With Large Doses of Morphine and Amiphenazole (Daptazole), Acta anaesth. scandinav. **2**:45-51, 1958.
68. Eddy, N. B., Halbach, H., and Braenden, O. J.: Synthetic Substances With Morphine-like Effect: Clinical Experience: Potency, Side Effects, Addiction Liability, Bull. World Health Organ. **17**:569-863, 1957.
69. Egbert, L. D., Norton, M. L., Eckenhoff, J. E., and Dripps, R. D.: A Comparison in Man of the Effects of Promethazine, Secobarbital and Meperidine Alone and in Combination on Certain Respiratory Functions and for Use

in Preanesthetic Medication, South. M. J. **51**:1173-1177, 1958.

70. Eisleb, O., and Schaumann, O.: Dolantin ein neuartiges Spasmolytikum und Analgetikum. Deutsche med. Wchnschr. **65**:967-968, 1939.
71. von Euler, C., and Söderberg, U.: Medullary Chemosensitive Receptors, J. Physiol. **118**:545-554, 1952.
72. Evans, A. G. J., Nasmyth, P. A., and Stewart, H. C.: The Fall of Blood Pressure Caused by Intravenous Morphine in the Rat and Cat, Brit. J. Pharmacol. **7**:542-552, 1952.
73. Fejfar, Z., Bergman, K., Fejfarova, M., and Valach, A.: The Effect of Morphine on Pulmonary Haemodynamics in Mitral Stenosis, Cardiologica **31**:461-468, 1957.
74. Feldberg, W., and Paton, W. D. M.: Release of Histamine From Skin and Muscle in the Cat by Opium Alkaloids and Other Histamine Liberators, J. Physiol. **114**:490-509, 1951.
75. Finer, B. L., and Partington, M. W.: Pethidine and the Triple Response, Brit. M. J. **1**:431-433, 1953.
76. Fink, L. D., and Akiyama, J.: Response of the Excised Guinea Pig Tracheal Muscle to Morphine and Meperidine, Arch. internat. pharmacodyn. **91**:322-329, 1952.
77. Fischer, J. W., and Dolehide, R. A.: Fatal Cardiac Failure in Persons With Thoracic Deformities, A.M.A. Arch. Int. Med. **93**:687-697, 1954.
78. Fischer, J. W., and Dolehide, R. A.: Hazard of Morphine in Kyphoscoliosis, J.A.M.A. **156**:1274, 1954.
79. Fishman, A. P., Turino, G. M., and Bergofsky, E. H.: Editorial—The Syndrome of Alveolar Hypoventilation, Am. J. Med. **23**:333-339, 1957.
80. Fjeldborg, N., and Johansen, S.: The Antagonism of N-allyl-n-desmethylmorphine to Pethidine, Danish. M. Bull. **3**:220-222, 1956.
81. Foldes, F. F., Duncalf, D., Robbins, R. S., D'Sousa, P. B., and Conte, A. A.: Production of Controllable Apnea in Anesthesia, J.A.M.A. **166**:325-331, 1958.
82. Foldes, F. F.: Narcotic-Induced Controllable Apnea, Am. J. M. Sc. **233**:1-3, 1957.
83. Foldes, F. F., and Ergin, K. H.: Levallorphan and Meperidine in Anesthesia, J.A.M.A. **166**:1453-1458, 1958.
84. Foldes, F. F., and Machaj, T. S.: Morphin—Antagonisten, Anesthesist. **6**:95-99, 1957.
85. Fraser, H. F.: Human Pharmacology and Clinical Uses of Nalorphine (N-allylnormorphine), M. Clin. North. America, pp. 1-11, March, 1957.
86. Fraser, H. F., and Isbell, H.: Chlorpromazine and Reserpine: The Effects of Each and of Combination of Each With Morphine, Arch. Neurol. & Psychiat. **76**:256-262, 1956.
87. Fraser, H. F., Van Horn, G. D., and Isbell, H.: Studies on N-allylnormorphine in Man: Antagonism to Morphine and Heroin and Effects of Mixtures of N-allylnormorphine and Morphine, Am. J. M. Sc. **231**:1-8, 1956.
88. Fraser, H. F., Wikler, A., Van Horn, G. D., Eisenman, A. J., and Isbell, H.: Human Pharmacology and Addiction Liability of Normorphine, J. Pharmacol. & Exper. Therap. **122**:359-369, 1958.
89. Gershon, S., and Shaw, F. H.: Morphine and Histamine Release, J. Pharm. & Pharmacol. **10**:22-29, 1958.
90. Giff, J. H. P.: Pethidine in Labour, Letter to Editor, Brit. M. J. **1**:901, 1947.
91. Gottsegen, G., Romoda, T., and Szám I.: Zum Mechanismus der Morphinwirkung bei Herzinsuffizienz und akutem Lungenödem, Ztschr. inn. Med. **11**:625-628, 1956.
92. Greisheimer, E. M., Ellis, D. W., Makarenko, L. I., and Stewart, G. H.: Effect of Morphine and Thiopental Sodium-Oxygen Upon Cardiovascular Function in the Dog, Anesthesiology **17**:798-801, 1956.
93. Greisheimer, E. M., Ellis, D. W., Makarenko, L. I., and Stewart, G. H.: Effect of Morphine and Cyclopropane Upon Cardiovascular Functions in the Dog, Anesthesiology **18**:196-202, 1957.
94. Gross, E. G., and Hamilton, W. K.: Preliminary Observations on the Effect of Levallorphan on Respiratory Depression and Analgesia of Levorphan in Man, J. Lab. & Clin. Med. **43**:938-941, 1954.
95. Gruber, C. M., Jr.: The Effect of N-allylnormorphine in the Presence of Secobarbital, J. Pharmacol. & Exper. Therap. **111**:409-412, 1954.
96. Gruhzit, C. C.: Chemoreflex Activity of Dextromethorphan (Romilar), Dextrorphan, Codeine, and Morphine in the Cat and Dog, J. Pharmacol. & Exper. Therap. **120**:399-407, 1957.
97. Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. McC., and Bradley, S. E.: The Renal and Hepatic Blood Flow, Glomerular Filtration Rate and Urinary Output of Electrolytes During Cyclopropane, Ether, and Thiopental Anesthesia, Operation and the Immediate Postoperative Period, Surgery **30**:241-255, 1951.
98. Hamilton, W. K., and Cullen, S. C.: Effect of Levallorphan Tartrate Upon Opiate Induced Respiratory Depression, Anesthesiology **14**:550-554, 1953.
99. Hamilton, W. K., and Cullen, S. C.: Supplementation of Nitrous Oxide Anesthesia With

Opiates and a New Opiate Antagonist, Anesthesiology **16**:22-28, 1955.

100. Hamilton, W. K., and Devine, J. C.: The Evaluation of Respiratory Adequacy in the Immediate Postoperative Period, Surg. Gynec. & Obst. **105**:229-232, 1957.
101. Harvey, W. P., Berkman, F., and Leonard, J.: Caution Against the Use of Meperidine Hydrochloride (Isomipecaine, Demerol) in Patients With Heart Disease, Particularly Auricular Flutter, Am. Heart J. **49**:758-769, 1955.
102. Helrich, M., Eckenhoff, J. E., Jones, R. E., and Rolph, W. D.: Influence of Opiates on the Respiratory Response of Man to Thiopental, Anesthesiology **17**:459-467, 1956.
103. Henderson, Y., and Scarbrough, M. McR.: Acapnia and Shock. VI. Acapnia as a Factor in the Dangers of Anesthesia, J. Physiol. **26**:260-286, 1910.
104. Henderson, Y.: Acapnia and Shock. IV. Fatal Apnea After Excessive Respiration, Am. J. Physiol. **25**:310-333, 1910.
105. Henriksen, E.: Morfin ag Asthma, Ugesk. laeger **113**:1158-1160, 1951.
106. Herxheimer, A., and Sanger, C.: Analgesic Action of Pethidine-Levallorphan Mixtures in Man, Brit. M. J. **2**:802-803, 1957.
107. Hibma, O. V., and Curreri, A. R.: A Study of the Effect of Morphine, Atropine and Scopolamine on the Bronchi, Surg. Gynec. & Obst. **74**:851-855, 1942.
108. Higgins, H. L., and Means, J. H.: The Effect of Certain Drugs on the Respiration and Gaseous Metabolism in Normal Human Subjects, J. Pharmacol. & Exper. Therap. **7**:1-15, 1915.
109. Hill, L.: The Influence of the Force of Gravity on the Circulation of Blood, J. Physiol. **18**:15-53, 1895.
110. Hill, H. E., Kornetsky, C. H., Flanary, H. G., and Wikler, A.: Effects of Anxiety and Morphine on Discrimination of Intensities of Painful Stimuli, J. Clin. Invest. **31**:473-480, 1952.
111. Hoff, H. E., and Breckenridge, C. G.: Intrinsic Mechanisms in Periodic Breathing, A.M.A. Arch. Neurol. & Psychiat. **72**:11-42, 1954.
112. Houde, R. W., and Wallenstein, S. L.: Clinical Studies of Morphine-Nalorphine Combinations, Fed. Proc. **15**:440-441, 1956.
113. Hove, H.: Morfin Forgiftning after Terapeutiske Morfin Doser, Ugesk. laeger **113**:1312-1313, 1951.
114. Huggins, R. A., Glass, W. G., and Bryan, A. R.: The Cardiovascular Effect of Some Narcotics, Arch. internat. pharmacodyn. **86**:112-120, 1951.
115. Huggins, R. A., and Moyer, J. A.: Some Effects of N-allylnormorphine on Normal Subjects and a Review of the Literature, Anesthesiology **16**:82-90, 1955.
116. Huggins, R. A., Seibert, R. A., and Bryan, A. R.: Comparison of Effects of Morphine and Barbital on Volume Distribution of Potassium, Am. J. Physiol. **168**:33-36, 1952.
117. Huggins, R. A., Spencer, W. A., Geddes, L. A., Deavers, S., and Moyer, J. H.: Respiratory Functions in Man Following Intravenous Administration of Morphine, N-allylnormorphine, N-allylnormorphine After Morphine, Arch. internat. pharmacodyn. **111**:275-292, 1957.
118. Irvin, C. W.: Valsalva Maneuver as a Diagnostic Aid, J.A.M.A. **170**:787-791, 1959.
119. Isbell, H., and Fraser, H. F.: Unpublished data but quoted by Fraser, H. F.: Human Pharmacology and Clinical Uses of Nalorphine, M. Clin. North America **41**:1-11, March, 1957.
120. Jeghers, H., and Brick, I. B.: Hazards in the Therapeutic Use of Morphine, M. Clin. North America **34**:1761-1777, 1950.
121. Johnstone, M.: Pethidine and General Anesthesia, Brit. M. J. **2**:943-946, 1951.
122. Jones, R. E., Price, H. L., Linde, H. W., and Dripps, R. D.: Cyclopropane. III. Effects of Cyclopropane on Respiration and Circulation in Man, Anesthesiology. In press.
123. Juhl, O., and Madsen, S.: Cor-Pulmonale-Morphine, Ugesk. laeger **117**:358-360, 1955.
124. Kalow, W.: The Distribution, Destruction and Elimination of Muscle Relaxants, Anesthesiology **20**:505-518, 1959.
125. Kalser, M. H., Frye, C. W., and Gordon, A. S.: Postural Hypotension Induced by Atropine Sulfate, Circulation **10**:413-422, 1954.
126. Katz, K. H., and Chandler, H. L.: Morphine Hypersensitivity in Kyphoscoliosis, New England J. Med. **238**:322-324, 1948.
127. Keats, A. S.: New Concepts in the Action of Analgesic Drugs, South. M. J. **49**:1285-1289, 1956.
128. Keats, A. S., and Beecher, H. K.: Analgesic Potency and Side Action Liability in Man of Heptazine, WIN 1161-2, 6-Methyl dihydromorphine, Metapon, Levoisomethadone and Pentobarbital Sodium, J. Pharmacol. & Exper. Therap. **105**:109-129, 1952.
129. Keats, A. S., and Mithoefer, J. C.: The Mechanism of Increased Intracranial Pressure Induced by Morphine, New England J. Med. **252**:1110-1113, 1955.
130. Keats, A. S., and Mithoefer, J. C.: Nature of Antagonism of Nalorphine to Respiratory Depression Induced by Morphine in Man, Fed. Proc. **14**:356-357, 1955.
131. Keats, A. S., Telford, J., and Kurosu, Y.:

Studies of Analgesic Drugs: Anileridine Dihydrochloride, Anesthesiology **18**:690-697, 1957.

132. Kepes, E. R., and Margolius, B. R.: The Effect of Nisentil Hydrochloride and Lorfan Tartrate on Respiration During Nitrous Oxide-Oxygen Anesthesia, Am. J. Surg. **91**:761-769, 1956.
133. Kety, S. S.: Human Cerebral Blood Flow and Oxygen Consumption as Related to Aging, J. Chron. Dis. **3**:478-486, 1956.
134. King, B. D., Elder, J. D., and Dripps, R. D.: The Effect of Intravenous Administration of Meperidine Upon the Circulation of Man and Upon the Circulatory Response to Tilt, Surg. Gynec. & Obst. **94**:591-597, 1952.
135. Krueger, H.: Narcotics and Analgesics, in Manske, R. H. F., editor: The Alkaloids: Chemistry and Physiology, New York, 1955, Academic Press, Inc., vol. 5, chap. 1.
136. Krueger, H., Eddy, N. B., and Sumwalt, M.: The Pharmacology of the Opium Alkaloids, Suppl. 165, Pub. Health Rep. 1941.
137. Lambertsen, C. J., and Wendel, H.: An Alveolar Carbon Dioxide Tension Control System. Its Use to Magnify Respiratory Depression by Merperidine, J. Appl. Physiol. **15**:43-48, 1960.
138. Lambertsen, C. J., Wendel, H. J., and Longenhagen, J. B.: The Separate and Combined Respiratory Effects of Chlorpromazine and Meperidine in Normal Men Controlled at 46 mm. Hg Alveolar PCO_2. In press.
139. Landmesser, C. M., Formel, P. F., and Converse, J. G.: Comparative Effects of a New Narcotic Antagonist (Levallorphan Tartrate) Upon the Respiratory Responses to Carbon Dioxide During Narcotic and Barbiturate Depression in Anesthetized Man, Anesthesiology **16**:520-535, 1955.
140. Lasagna, L.: Nalorphine (N-allylnormorphine) Practical and Theoretical Considerations, A.M.A. Arch. Int. Med. **94**:532-558, 1954.
141. Lasagna, L., and Beecher, H. K.: The Analgesic Effectiveness of Nalorphine and Nalorphine-Morphine Combinations in Man, J. Pharmacol. & Exper. Therap. **112**:356-363, 1954.
142. Lear, E., Chiron, A. E., and Pallin, I. M.: Chlorpromazine—An Adjunct to Premedication, New York J. Med. **55**:1853-1857, 1955.
143. Lee, R. E., and Zweifach, B. W.: Vasodepressor Responses to Morphine Following Hemorrhagic Hypotension, Am. J. Physiol. **157**:259-264, 1949.
144. Liljestrand, A.: Neural Control of Respiration, Physiol. Rev. **38**:691-708, 1958.
145. Lipson, H. I., and Bradford, H. R.: Alphaprodine (Nisentil) Hydrochloride in Anesthesia, J.A.M.A. **163**:1244-1248, 1957.
146. Loeschke, H. H., Sweel, A., Kough, R. H., and Lambertsen, C. J.: The Effect of Morphine and of Meperidine (Dolantin, Demerol) Upon the Respiratory Response of Normal Men to Low Concentrations of Inspired Carbon Dioxide, J. Pharmacol. & Exper. Therap. **108**:376-383, 1953.
147. Loeschke, H. H., and Wendel, H.: Die Wirkung von Morphin, von Scopolamin und ihrer Kombination auf die Lungenbelüftung beim Menschen, Arch. Exper. Path. u. Pharmacol. **215**:241-255, 1952.
148. Loewy, A.: Zur Kenntnis Erregbarkeit des Athemcentrums, Pflügers. Arch. **47**:601-621, 1890.
149. Loewy, A.: Ueber den Einfluss einiger Schlafmittel auf die Erregbarkeit des Athemcentrums nebst Beobachtungen über die Intensität des Gaswechels im Schlafe beim Menschen, Berl. klin. Wchnschr. **28**:434-438, 1891.
150. Lyngar, A. E.: Status Asthmaticus og Morfin, Tidsskr. norske. laegefor. **72**:131, 1952.
151. McCall, M. L., and Taylor, H. W.: Effects of Morphine Sulfate on Cerebral Circulation and Metabolism in Normal and Toxemic Pregnant Women, Am. J. Obst. & Gynec. **64**:1131-1136, 1952.
152. McDermott, T. F., and Papper, E M.: Respiratory Complications Associated Demerol, New York J. Med. **50**:1721-1 1950.
153. Macintosh, R. R.: Lumbar Pur e and Spinal Analgesia, Baltimore, 1951, lliams & Wilkins Company, p. 59.
154. Malt, R. A.: Effect of Preanesthetic dication on Cardiovascular Force, Anes iology **19**:353-358, 1958.
155. Mannering, G. J., and Takemori, A. E.: Demethylation of Narcotic Drugs and the Phenomenon of Tolerance, Fed. Proc. **17**:391, 1958.
156. Margolius, B. R., and Kepes, E. R.: Meperidine-Levallorphan in Anesthesia, Am. J. Surg. **95**:787-792, 1958.
157. Marshall, E. K., Jr., and Rosenfeld, M.: Depression of Respiration by Oxygen, J. Pharmacol. & Exper. Therap. **57**:437-457, 1936.
158. May, A. J., and Widdicombe, J. G.: Depression of the Cough Reflex by Pentobarbitone and Some Opium Derivatives, Brit. J. Pharmacol. **9**:335-340, 1954.
159. May, G., Phillips, M., and Adriani, J.: Effect of N-allylnormorphine and Levallorphan on Respiration During and After Ether Anesthesia, Anesthesiology **18**:871-877, 1957.
160. Megirian, R., and White, C. W.: An Evaluation of the Respiratory and Sedative Effects of Meperidine HCl Combined With Leval-

lorphan Tartrate in Postoperative Patients, New England J. Med. **257**:849-855, 1957.

161. Megirian, R., White, C. W., and Marcus, P. S.: Alphaprodine Hydrochloride With Levallorphan Tartrate or RO 1-7780 Postoperatively, Anesthesiology **18**:610-622, 1957.
162. Meyer, O., and Oehmig, H.: Die Wirkung der Opiatantagonisten (-)-3-oxy-N-allyl-Morphinan-tartrat (Levallorphan RO 1-7700) und N-allylnormorphin am narkotisierten Menschen, Anaesthesist. **5**:4-7, 1956.
163. Meyler, L.: Versterkte Gevoeligheid voor Opiaten en Barbiturzuren bij Anoxie, Nederl. tijdschr. geneesk. **94**:2467-2470, 1950.
164. Miller, R. D., Kalser, M. H., Frye, C. W., and Gordon, A.: Measurement of Atropine Induced Vascular Pooling, Circulation **10**:423-429, 1954.
165. Mitchell, H. S., and Cooke, W. R.: Studies on the Effect of Morphine and Related Compounds on Bronchial Muscle, Canad. M. A. J. **73**:45-46, 1955.
166. Mitchell, H. S., and DeJong, J. D.: The Effect of Morphine on Bronchial Muscle, J. Allergy **25**:302-305, 1954.
167. Moller, K. O.: Dod Fremkaldt Med Terapeutiske Doser af Marfin Eller Morfin—Skopolamin Hos Alkoholpavirkede Eller Barbiturayre Pavirkede Personer, Ugesk. laeger **114**:1785-1793, 1952.
168. Monroe, R. T.: Diseases in Old Age, Harvard Univ. Monographs in Medicine and Public Health No. 11, Cambridge, Mass., 1951, Harvard University Press.
169. Moyer, J. H., Morris, G. C., and Pontius, R. G.: Effect of Morphine and N-allylnormorphine on Cerebral Hemodynamics and Cerebral Oxygen Metabolism as Compared to Similar Observations on Chlorpromazine When Administered to Man, M. Rec. & Ann. **50**:62-65, 1956.
170. Murano, T., and Tanaka, F.: Possible Roles of the Central Nervous System in the Action of Morphine on Blood Pressure, Jap. J. Pharmacol. **6**:94-104, 1957.
171. Nussbaum: Bavarian Medical Intelligencer, 1863, quoted by Reeves, J. C.: On Modification of Anesthetic Processes by Hypodermic Injection of Narcotics, Am. J. M. Sc. **71**:374, 1876.
172. Orahovats, P. D., Winter, C. A., and Lehman, E. G.: Pharmacological Studies of Mixtures of Narcotics and N-allylnormorphine, J. Pharmacol. & Exper. Therap. **112**:246-251, 1954.
173. Orkin, L. R., Egge, R. K., and Rovenstine, E. A.: Effect of Nisentil, Meperidine and Morphine on Respiration in Man, Anesthesiology **16**:699-707, 1955.
174. Orton, R. H., Peacock, H., and Phillips, G.: Allyly-nor-morphine, Anaesthesia **9**:88-91, 1954.
175. Papper, E. M., and Bradley, S. E.: Hemodynamic Effects of Intravenous Morphine and Pentothal Sodium, J. Pharmacol. & Exper. Therap. **74**:319-323, 1942.
176. Paterson, S. J., and Prescott, F.: Nalorphine in the Prevention of Neonatal Asphyxia Due to Maternal Sedation With Pethidine, Lancet **1**:490-493, 1954.
177. Paton, W.D.M.: Possible Causes of Prolonged Apnoea, Anaesthesia **13**:253-268, 1958.
178. Payne, J. P.: The Effects of N-allylnormorphine in Healthy Subjects Premedicated With Morphine, Brit. J. Anaesth. **26**:22-25, 1954.
179. Peterson, L. H., Eather, K. F., and Dripps, R. D.: Postural Changes in the Circulation of Surgical Patients as Studied by a New Method for Recording the Arterial Blood Pressure and Pressure Pulse, Ann. Surg. **131**:23-30, 1950.
180. Pettus, W. W., Geiger, A. J., and Grezebien, S. T.: Effects of Morphine on the Electrocardiogram of Men, Yale J. Biol. & Med. **14**:493-500, 1942.
181. Pickering, R. W., Abrey, B. E., Bohr, D. F., and Reynolds., W. F.: Some Effects of Meperidine (Demerol) on Gastro-enteric, Extrahepatic Biliary, and Cardiovascular Activity, J. Am. Pharm. A. **38**:188-192, 1949.
182. Porges, O., and Kauders, F.: Die Gefahren des Morphiums bei Dyspnoe, Wien. med. Wchnschr. **72**:533-535, 1922.
183. Prescott, F., Ransom, S. G., Thorp, R. H., and Wilson, A.: Effects of Analgesics on Respiratory Response to Carbon Dioxide in Man, Lancet **1**:340-342, 1949.
184. Price, H. L.: A Dynamic Concept of the Distribution of Thiopental in the Human Body, Anesthesiology **21**:40-45, 1960.
185. Price, H. L., Kovnat, P. J., Safar, J. N., Conner, E. H., and Price, M. L.: The Uptake of Thiopental by Body Tissues and Its Relation to the Duration of Narcosis, CLIN. PHARMACOL. & THERAP. **1**:16-22, 1960.
186. Prime, F. J., and Westlake, E. K.: The Respiratory Response to Carbon Dioxide in Emphysema, Clin. Sc. **13**:321-332, 1954.
187. Reckless, D.: Action of Chlorpromazine and Promethazine, Brit. M. J. **1**:1035-1036, 1954.
188. Reed, D. J., and Kellog, R. H.: Changes in Respiratory Response to CO_2 During Natural Sleep at Sea Level and at Altitude, J. Appl. Physiol. **13**:325-330, 1958.
189. Remy, D., and Wolsky, H.: Der Einfluss von Polamidon (Hoechst 10820) im Vergleich zu Morphine und Dolantin auf die Ventilationsgrösse unter Kohlensäureatmung Chem. Zentralbl. **2**:316, 1950.

190. Reynolds, A. K., and Randall, L. O.: Morphine and Allied Drugs, Toronto, 1957, University of Toronto Press.
191. Richter, T., West, J. R., and Fishman, A. P.: Syndrome of Alveolar Hyperventilation and Diminished Sensitivity of Respiratory Center, New England J. Med. **256**:1165-1170, 1957.
192. Richterich, R., Baerle, Van, and Byrnes, W. W.: Die pharmakologische und klinische Bedentung der Morphin-Antagonisten, Ztschr. inn. Med. **10**:1017-1030, 1955.
193. Roberts, H., Kane, K. M., Percival, N., Snow, P., and Please, N. W.: Effects of Some Analgesic Drugs Used in Childbirth, Lancet **1**:128-132, 1957.
194. Robin, E. D., Whaley, R. D., Crump, C. H., and Travis, D. M.: Alveolar Gas Tensions, Pulmonary Ventilation and Blood pH During Physiologic Sleep in Normal Subjects, J. Clin. Invest. **37**:981-989, 1958.
195. Robson, J. M., and Keele, C. A.: Recent Advances in Pharmacology, Boston, 1956, Little, Brown and Company.
196. Roussak, N. J.: Lethal Effect of Morphine in Chronic Cor Pulmonale, Lancet **1**:1156-1157, 1951.
197. Rovenstine, E. A., and Cullen, S. C.: The Anesthetic Management of Patients With a Hyperactive Carotid Sinus Reflex, Surgery **6**:167-176, 1939.
198. Sadove, M. S., Schiffrin, M. J., Nickerson, W. R., and Grove, W. J.: Use of Meperidine and Meperidine-Levallorphan Mixtures in the Recovery Room, J.A.M.A. **166**:1432-1437, 1958.
199. Salomon, A., Marcus, P. S., Herschfus, J. A., and Segal, M. S.: N-allylnormorphine (Nalline) Action in Narcotized and Non-narcotized Subjects, Am. J. Med. **17**:214-222, 1954.
200. Samúelsson, S.: The Danger of Using Morphine in Cor Pulmonale, Cardiologia **21**:817-825, 1952.
201. Scarborough, W. R.: Some Circulatory Effects of Morphine-Barbiturate Anesthesia, Artificial Respiration and Abdominal Compression on Ballistocardiographic Observations in Dogs, Am. Heart J. **54**:651-677, 1957.
202. Scebat, L., and Lenègre, I.: L'Action de la morphine sur la pression sanguine des cavités droites du coeur chez les cardiaques, Arch. mal. coeur **42**:1154-1156, 1949.
203. Schachter, M.: The Release of Histamine by Pethidine, Atropine, Quinine and Other Drugs, Brit. J. Pharmacol. **7**:646-654, 1952.
204. Schaumann, O.: Morphin und morphinähnlich wirkende Verbindungen, in Handbuch der experimentellen Pharmakologie, Zwölfter Band, Berlin, 1957, Springer-Verlag.
205. Schiffrin, M. J., Balagot, R. C., and Sadove, M. S.: Some Effects of Levallorphan on Responses to Meperidine, Canad. Anaes. Soc. J. **4**:372-377, 1957.
206. Schmidt, C. F., and Livingston, A. E.: The Action of Morphine on the Mammalian Circulation, J. Pharmacol. & Exper. Therap. **47**:411-441, 1933.
207. Schoen, R.: Untersuchungen über die zerebrale Innervation der Atmung. I. Mitteilung, Arch. Exper. Path. u. Pharmakol. **135**:155-187, 1928.
208. Schuman, E. A., and McCall, M. I.: Morphine-Scopolamine for Vaginal Operations in Older Women, Obst. & Gynec. **2**:266-267, 1953.
209. Seed, J. C., Wallenstein, S. L., Houde, R. W., and Bellville, J. W.: A Comparison of the Analgesic and Respiratory Effects of Dihydrocodeine and Morphine in Man, Arch. internat. pharmacodyn. **116**:293-339, 1958.
210. Seevers, M. H., and Woods, L. A.: The Phenomenon of Tolerance, Am. J. Med. **14**:546-557, 1953.
211. Severinghaus, J. W., and Stupfel, M.: Respiratory Dead Space Increase Following Atropine in Man, and Atropine, Vagal or Ganglionic Blockade and Hypothermia in Dogs, J. Appl. Physiol. **8**:81-87, 1955.
212. Shemano, I., Wendel, H., and Katinsky, H.: Personal communication.
213. Siker, E. S., Brunn, H. M., Crawford, J. S., and Foldes, F. F.: The Circulatory Effects of Narcotics and Narcotic Antagonists in Man, Anesthesiology **21**:115-116, 1960.
214. Slavin, M. I.: Demerol Premedication in the Ambulatory Patient, Oral Surg., Oral Med. and Oral Path. **3**:1159-1167, 1950.
215. Slome, D.: The Nervous Control of Respiration, Ann. Roy. Col. Surgeons **9**:318-332, 1951.
216. Smythe, C. M., and Gilmore, J. P.: The Effect of Morphine on Hepatic Blood Flow in the Normal Anesthetized Dog, J. Pharmacol. & Exper. Therap. **114**:221-224, 1955.
217. Sokoloff, L.: Action of Drugs on the Cerebral Circulation, Pharmacol. Rev. **11**:1-86, 1959.
218. Spain, D. M., and Handler, B. J.: Chronic Cor Pulmonale, Arch. Int. Med. **77**:37-65, 1946.
219. Starr, I., Gamble, C. J., Margolies, A., Donal, J. S., Joseph, N., and Eagle, E.: A Clinical Study of the Action of 10 Commonly Used Drugs on Cardiac Output, Work and Size; on Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin Invest. **16**:799-823, 1937.
220. Steinberg, S. S., Bellville, J. W., and Seed, J. C.: The Effect of Atropine and Morphine on Respiration, J. Pharmacol. & Exper. Therap. **121**:71-77, 1957.
221. Stoelting, V. K., and Hicks, M. L.: Com-

bined Use of Narcotics and Narcotic Antagonist in the Supplementation of Anaesthesia, Canad. Anaesth. Soc. J. **3**:107-112, 1956.

222. Stone, H. H., Mackrell, T. N., Brandstater, B. J., Haidak, G. L., and Nemir, P.: The Effect of Induced Hemorrhagic Shock on the Cerebral Circulation and Metabolism of Man, S. Forum **5**:789-794, 1954.
223. Stroud, M. W., Lambertsen, C. J., Ewing, J. H., Kough, R. H., Gould, R. A., and Schmidt, C. F.: The Effects of Aminophylline and Meperidine Alone and in Combination on the Respiratory Response to Carbon Dioxide Inhalation, J. Pharmacol. & Exper. Therap. **114**:461-469, 1955.
224. Sugioka, K., Boniface, K. J., and Davis, D. A.: The Influence of Meperidine on Myocardial Contractility in the Intact Dog, Anesthesiology **18**:623-633, 1957.
225. Swerdlow, M.: The Respiratory Effects of Pethidine and Levallorphan, Anaesthesia **12**:174-181, 1957.
226. Swerdlow, M.: Dihydrocodeine, Lancet **1**:482-485, 1957.
227. Swerdlow, M.: Levallorphan, Anaesthesia **12**:318-323, 1958.
228. Swerdlow, M., Foldes, F. F., and Siker, E. S.: The Effects of Nisentil HCl (Alphaprodine HCl) and Levallorphan Tartrate on Respiration, Am. J. M. Sc. **230**:237-250, 1955.
229. Swerdlow, M., and Newman, J.: Some Effects of Premedication, Brit. J. Anaesth. **29**:66-70, 1957.
230. Taquini, A. C., Roncoroni, A. J., Aramendía, P., and Ros, A. M.: Sensitivity of Respiratory Center to Carbon Dioxide in Emphysema and Cor Pulmonale: Effects of Carbonic Anhydrase Inhibition, Am. Heart J. **54**:319-341, 1957.
231. Taterka, H., and Pinéas, H.: Beiträge zun Problem des Atemstillstandes bei Tabes dorsalis, Nervenarzt **1**:543, 1928.
232. Taussig, H. B.: Tetralogy of Fallot. Especially the Case of the Cyanotic Infant and Child, Pediatrics **1**:307-314, 1948.
233. Taylor, H. E., Doerr, J. C., Gharib, A., and Faulconer, A.: Effect of Preanesthetic Medication on Ether Content of Arterial Blood Required for Surgical Anesthesia, Anesthesiology **18**:849-855, 1957.
234. Tenney, S. M.: Mechanism of Hypertension During Diffusion Respiration, Anesthesiology **17**:768-776, 1956.
235. Tenney, S. M., and Miller, R. M.: Respiratory Response in the Aged, J. Am. Geriat. Soc. **3**:937-944, 1955.
236. Tenney, S. M., and Miller, R. M.: Dead Space Ventilation in Old Age, J. Appl. Physiol. **9**:321-327, 1956.
237. Tenney, S. M., and Mithoefer, J. C.: The Respiratory Depressant Action of N-allylnormorphine in the Normal Subject and in Patients With Respiratory Acidosis Secondary to Pulmonary Emphysema, New England J. Med. **249**:886-890, 1953.
238. Thomas, D. V., and Tenney, S. M.: The Effect of Levorphan and Levallorphan on the Respiratory Mechanism of Normal Man, J. Pharmacol. & Exper. Therap. **113**:250-255, 1955.
239. Unger, L.: Bronchial Asthma, Springfield, Ill., 1945, Charles C Thomas, Publisher.
240. Van Arman, C. G., and Sturtevant, F. M.: Release of Histamine by Meperidine, Fed. Proc. **17**:416, 1958.
241. Vaughan, W. T., and Graham, W. R.: Death From Asthma, J.A.M.A. **119**:556-557, 1942.
242. Vivante, A., Kao, F., and Belford, J.: The Effect of Nalorphine on the Respiration of Dogs Anesthetized With Pentobarbital Sodium, J. Pharmacol. & Exper. Therap. **111**:436-446, 1954.
243. Wallenstein, S. L., Bellville, J. W., and Houde, R. W.: The Respiratory Effects of Levorphan and Levallorphan in Man, Fed. Proc. **17**:417, 1958.
244. Walton, C.H.A., Penner, D. W., and Wilt, J. C.: Sudden Death From Asthma, Canad. M. A. J. **64**:95-102, 1951.
245. Wangeman, C. P., and Hawk, M. H.: The Effects of Morphine, Atropine and Scopolamine on Human Subjects, Anesthesiology **3**:24-36, 1942.
246. Waters, R. M.: A Study of Morphine, Scopolamine and Atropine and Their Relation to Preoperative Medication and Pain Relief, Texas J. Med. **34**:304-305, 1938.
247. Waters, R. M., and Hawk, M. H.: Morbidity Accompanying the Therapy of Pain. The Cost of Comfort, Surgery **12**:450-458, 1942.
248. Weakley, L. S., and Bergner, R. P.: The Respiratory Effects of N-allylnormorphine in Secobarbital Sodium Narcosis, Anesthesiology **18**:603-609, 1957.
249. Weimann, G., and Hermanuz, N.: Zur Wirkung von Dihydromorphinon-Atropin auf die Atmug, Anaesthesist **8**:351-353, 1959.
250. Weinberg, S. J., and Sensiba, S. W.: Scopolamine-Methadone-Demerol Treatment of Emergency Status Asthmaticus, Dis. Chest **30**:580-582, 1956.
251. Weiss, S., Wilkins, R. W., and Haynes, F. W.: The Nature of Circulatory Collapse Induced by Sodium Nitrate, J. Clin. Invest. **16**:73-84, 1937.
252. Wells, R. E.: Mechanics of Respiration in Bronchial Asthma, Am. J. Med. **26**:384-393, 1959.

253. Wendel, H., and Lambertsen, C. J.: Mechanism of Action of N-allylnormorphine in Morphine Induced Respiratory Depression in Man, Fed. Proc. **15**:497-498, 1956.
254. Wendel, H., and Lambertsen, C. J.: Morphine and Meperidine as Respiratory Depressants in Man, Fed. Proc. **16**:345, 1957.
255. Wikler, A.: Sites and Mechanism of Action of Morphine and Related Drugs in the Central Nervous System, Pharmacol. Rev. **2**:435-506, 1950.
256. Wikler, A., and Carter, R. L.: Effects of Single Doses of N-allylnormorphine on Hindlimb Reflexes of Chronic Spinal Dogs During Cycles of Morphine Addiction, J. Pharmacol. & Exper. Therap. **109**:92-101, 1953.
257. Wikler, A., Fraser, H. F., and Isbell, H.: N-allylnormorphine: Effects of Single Doses and Precipitation of Acute "Abstinence Syndrome" During Addiction to Morphine, Methodone or Heroin in Man (Postaddicts), J. Pharmacol. & Exper. Therap., **109**:8-20, 1953.
258. Wilkins, R. W., Haynes, F. W., and Weiss, S.: The Role of the Venous System in Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Invest. **16**:85-91, 1937.
259. Wilson, R. H., Hoseth, W., and Dempsey, M. E.: Respiratory Acidosis, Am. J. Med. **17**:464-484, 1954.
260. Woods, L. A.: The Pharmacology of Nalorphine (N-allylnormorphine), Pharmacol. Rev. **8**:175-198, 1956.
261. Woods, L. A.: Comparative Distribution of Morphine and Nalorphine in Dog Brain, J. Pharmacol. & Exper. Therap. **120**:58-62, 1957.
262. Zuck, D.: A Case of Pethidine Sensitivity. Brit. M. J. **1**:125, 1951.

The use of steroidal substances in endometriosis

Unfortunately, endometriosis seems to be occurring with increasing frequency, especially in women who marry late or in whom childbearing is deferred. Surgery may provide palliation but, unless castration is performed, recurrence is common. Recent efforts to treat this malady by hormonal methods have been successful.

The symptoms and signs of endometriosis disappear during pregnancy and remain in abeyance for many months thereafter. Persistent ovulation and menstruation aggravate the process. The physician may induce periods of prolonged anovulation with estrogens or estrogens combined with progestogens (pseudopregnancy). A decidual change is produced in areas of endometriosis similar to that seen in normal pregnancy. Subsequent necrosis and absorption of the decidua are postulated as the mechanism of producing objective improvement. Androgens, in low dosage, do not inhibit ovulation but seem to produce subjective and objective improvement. Methods of administration, side effects, and pharmacology of these steroidal substances are discussed in detail.

Robert W. Kistner, M.D. *Boston, Mass.*
Department of Obstetrics and Gynecology, Harvard Medical School, Boston, and the Free Hospital for Women, Brookline, Mass.

Endometriosis may be defined as the presence of functioning endometrial tissue outside of its normal situation but usually confined to the pelvis in the region of the ovaries, uterosacral ligaments, and uterovesical peritoneum. The characteristic symptoms of this disease are progressive, increasingly severe pelvic pain associated with, or occurring prior to, menstruation. Dyspareunia or rectal pain and tenesmus may accompany the menses. The crippling characteristics of this malady, occurring during the reproductive period of women, prevent fulfillment of marital potential since sexual intercourse is often painful and childbearing frequently impossible. Definitive treatment has too often been surgical, chiefly hysterectomy and castration, with the development of occasional neuroses and occasional psychoses. Although endometriosis is in reality a benign disease, it presents many of the characteristics of malignancy. Thus it may spread laterally to involve and encompass the ureter, producing stenosis and obstruction. It may, by direct extension, distort the serosa and muscularis of the sigmoid colon, producing bowel obstruction. The bladder may be involved in a similar process, resulting in symptoms of cyclic dysuria, urgency, and suprapubic

discomfort. The most frequently affected areas are the ovary and the posterior cul-de-sac. Complete destruction of the ovary by a large endometrioma is not infrequently seen and occasionally these large blood-filled cysts rupture with serious consequences. Infertility is a common finding in this disease and has been reported to occur in about one third of all patients whose primary complaint is that of infertility.

The process of pregnancy seems to have some protective effect on the development of endometriosis. This has been observed by numerous authors and in 1949 Meigs[9] suggested a method of prophylaxis against endometriosis: "early marriage and early childbearing." He even exhorted parents to subsidize their sons and daughters so that this might be financially feasible. He stated at that time: "It is the author's belief that avoidance of endometriosis through early marriage and frequent childbearing is the most important method of prophylaxis."

In many patients with this disease, however, conception is not always possible either because of unknown factors producing infertility or because marriage is not contemplated. The management of these patients must, however, be highly individualized because of the multiplicity of problems in diagnosis and the varying methods of therapy now available. Patients with minimal evidence of disease may be adequately managed by simple analgesia and observation. Others, with more extensive disease, should be subjected to operation but the procedure should be conservative with the preservation of childbearing function. An alternate method of therapy combines hormones with conservative surgery. In many patients with recurrent endometriosis hormonal methods alone may be utilized. Finally, in the most extensive cases or where childbearing function need not be preserved, hysterectomy and bilateral salpingo-oophorectomy should be performed. Preservation of an ovary may result in persistent ovulation and reactivation of the endometriosis.

Suppression of ovulation

Pregnancy has frequently been suggested as optimum prophylactic and therapeutic treatment for endometriosis, since both symptoms and signs regress during the period of gestation and for varying periods of time thereafter. This is probably due to a combination of anovulation and amenorrhea brought about by suppression of the adenohypophysis. In 1957 the author suggested that the improvement noted during pregnancy may also be due, in part, to a transformation of functioning endometriotic tissue into decidua by the increasing levels of estrogen and progesterone secreted by the placenta. If pregnancy is not contemplated or is not desired, it is possible to secure anovulation by the administration of various steroidal substances. Estrogens and androgens have been employed frequently for this purpose. Recently a newer treatment method utilizing synthetic progestins in combination with varying amounts of estrogen has been used and has given favorable results. The following therapeutic regimens have proved successful in most cases of endometriosis.

Estrogens. One milligram of diethylstilbestrol may be given on the first day of the menstrual period and is then increased by 1 mg. every 3 days to a total of 5 mg. daily. A 25 mg. tablet may then be prescribed and the dose is increased by one-fourth tablet (6.25 mg.) every 3 days until a total daily dose of 100 mg. is being administered. This should be continued for at least 3 months. The dose is then diminished in the same fashion so that abrupt cessation of estrogen stimulation is avoided. The gradual increase prevents the development of "break-through" bleeding and the gradual diminution in dose avoids, in most patients, profuse withdrawal bleeding.

The effectiveness of estrogen therapy depends upon the production of anovulation, amenorrhea, and a softening of the entire genital tract. It has been suggested by Karnaky[6] that areas of endometriosis undergo a state of "exhaustion atrophy." This theory, however, was not borne out in the experi-

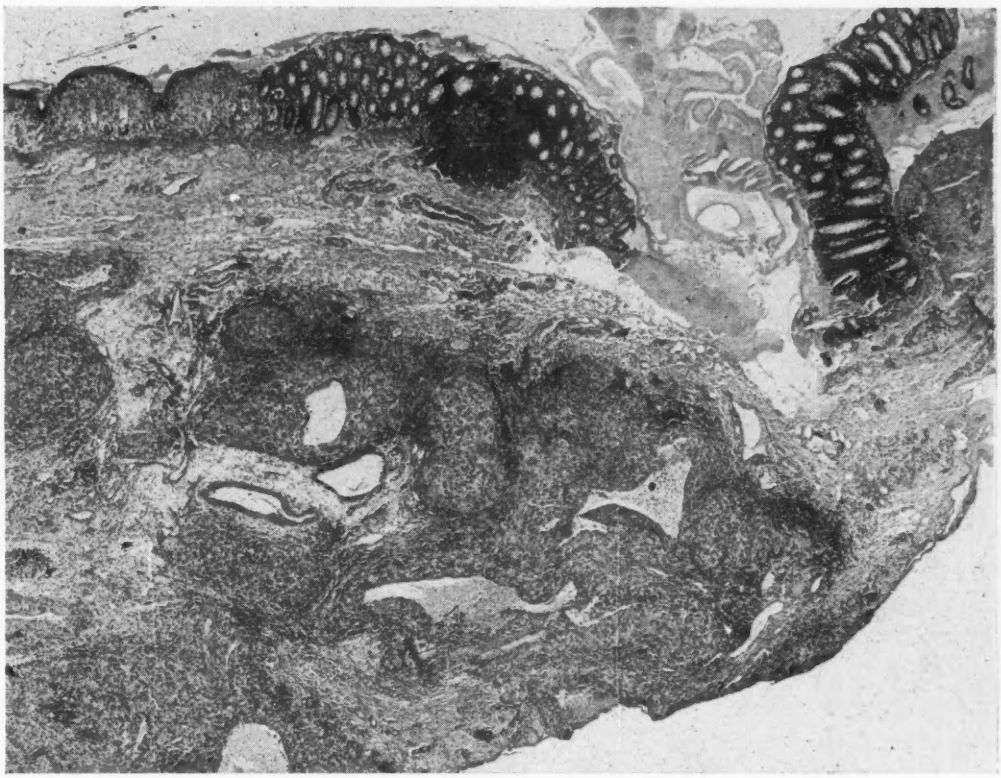


Fig. 1. FHW S-59-4561. Photomicrograph of a biopsy of a mass in the rectovaginal septum during the fourteenth week of pregnancy. Rectal mucosa is seen at the top of the section. Approximately two-thirds of the rectal wall has been replaced by endometriotic tissue made up of inactive glands and decidua. The endometrial stroma (as decidua) seems packed in "whorl-like" accumulations. (×40; reduced 1/6.)

ments of Scott[11] who administered constant doses of estrogens to macaque monkeys for prolonged periods. Exhaustion atrophy was not described at the termination of therapy and, in many subjects, actual hyperplasia was noted in the areas of endometriosis.

The side effects of estrogen therapy are early nausea, breast soreness, vaginal discharge, and occasional "break-through" bleeding. In most patients, however, these side effects are well tolerated or become less noticeable as therapy is continued. Beecham[2] has stated that "the physiological amenorrhea of pregnancy or the pregnancy equivalent induced by stilbestrol has produced regressive changes so remarkable that operative treatment once endorsed by all gynecologists is declining in popularity and usage."

Androgens. The usual scheme is to administer 10 mg. of methyltestosterone daily by mouth for two menstrual cycles and then omit for one cycle. An alternate method is to administer 5 mg. of methyltestosterone daily, sublingually, for 100 consecutive days. Ovulation is usually not inhibited and some gynecologists and endocrinologists have labeled the doses "homeopathic." This may be true in the male but in the female even small doses may be effective. Menstrual periods continue and pregnancy has been reported to have occurred while patients are taking methyltestosterone. This method has the disadvantage of occasionally producing masculinization of the female fetus if given during the period of organogenesis. The salutary effects of small doses are presumed to be due to the direct

action of androgens on areas of endometriosis. No microscopic evidence has been presented to show these changes. Higher dosages of methyltestosterone will inhibit ovulation and cause involution and suppression of follicular growth but amounts exceeding 300 mg. monthly may cause masculinizing symptoms in the adult female.

Side effects, especially in sensitive individuals, include acne, hoarseness, edema, hirsutism, enlargement of the clitoris, and hepatocellular jaundice. If acne appears as the first side effect, as it usually does, therapy with androgens should be stopped immediately and another therapeutic method substituted.

Progestins. In 1959 the author[7] reported the results of treatment in 58 patients utilizing combinations of estrogens with newer progestins given from 6 to 9 months. This concept of therapy was predicated on the fact that pregnancy usually brings about both objective and subjective improvement in patients with extensive pelvic endometriosis. Thus, a state of "pseudopregnancy" was brought about by gradually increasing the amounts of both estrogenic and progestrogenic substances. This seemed to be of particular value when the patient was infertile, did not desire pregnancy, or was unmarried. It was further suggested that the changes brought about in endometriosis by pregnancy are a combination of: (1) anovulation and amenorrhea, (2) decidual transformation of functioning endometriotic tissue, and (3) decidual necrosis and absorption. Figs. 1 and 2 demonstrate the effects of endogenous estrogen and progesterone on a large rectovaginal mass which was biopsied during the fourteenth week of an apparently normal pregnancy. The low-power view shows an extensive area of endometriosis under the rectal mucosa and the details of decidua formation are easily seen in the higher magnification.

A morphologically similar decidual reaction can be brought about both in the endometrium and in areas of endometriosis by the prolonged administration of estrogens and progestins. Fig. 3 illustrates an endometrial biopsy obtained after 4 weeks' administration of increasing 17-alpha-hydroxyprogesterone caproate and 8 weeks' of diethylstilbestrol. A marked transformation of the stromal cells together with glandular regression has occurred. As the pseudopregnancy is continued marked stromal edema occurs after 12 to 14 weeks. Fig. 4 demonstrates this change in an endometrial biopsy taken after 15 weeks of continuous estrogen-progestin therapy. Examination of the biopsy disclosed that there is marked edema at the surface, moderate decidual necrosis in the mid-zone, and a well-maintained decidua in the basalis. One atrophic gland is present in the right lower portion. It is suggested that the decidual cells undergo a gradual process of necrosis which is followed subsequently by liquefaction and absorption. This process is

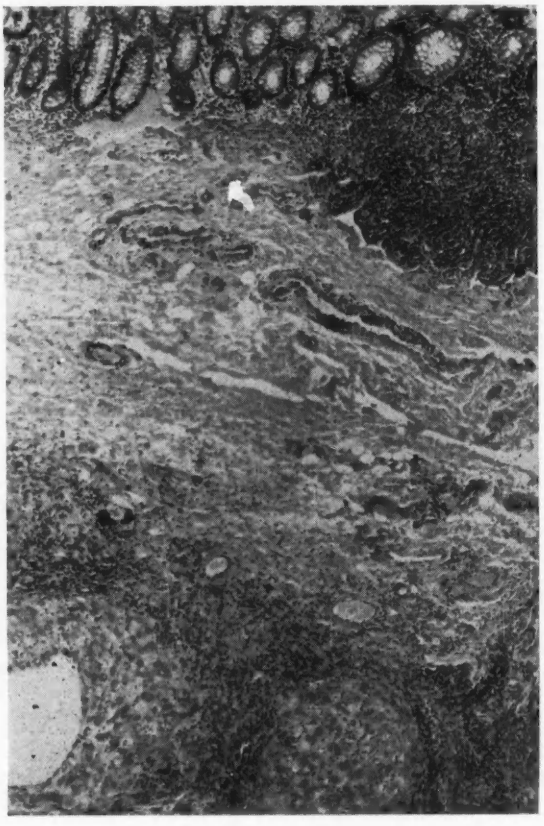


Fig. 2. FHW S-59-4561. Higher power of Fig. 1 to show detail of decidua and gland encroaching upon the submucosa of the rectum. (×100; reduced 1/3.)

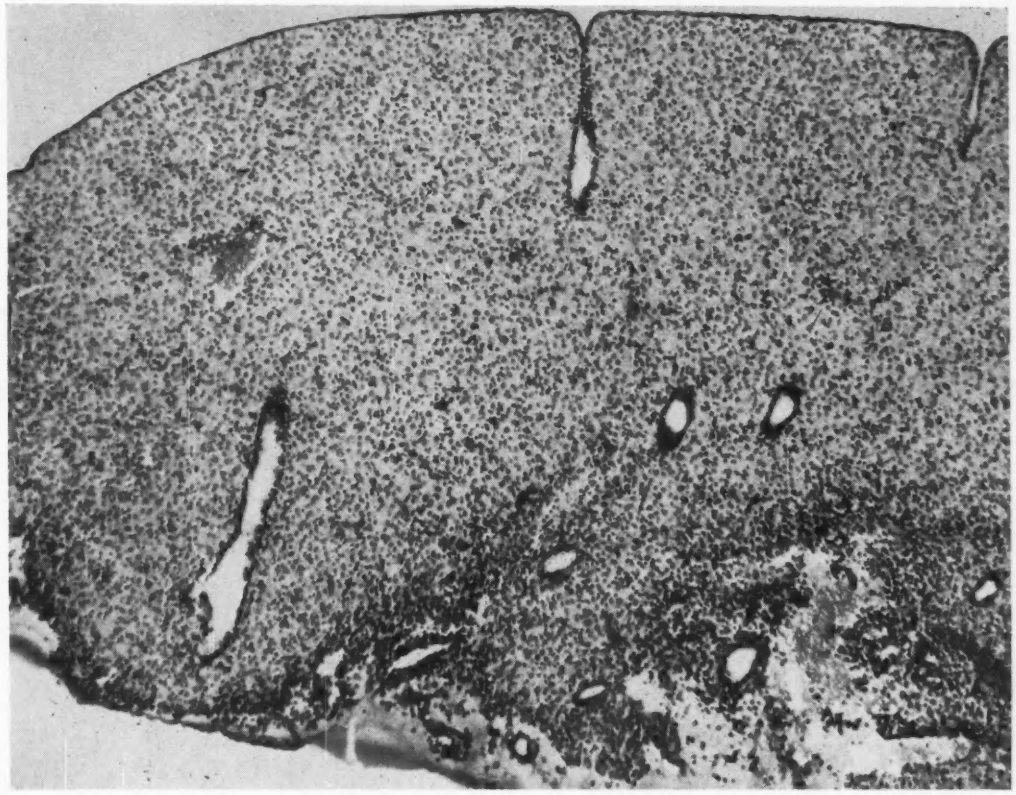


Fig. 3. FHW S-56-2835. Photomicrograph of an endometrial biopsy taken after 8 weeks of daily diethylstilbestrol and 4 weeks of 17-alpha-hydroxyprogesterone caproate pseudopregnancy. There is a well-developed decidual reaction throughout the stroma with several foci showing decidual necrosis. The glands have the typical "arrested" appearance noted after the use of large doses of progestogenic substances. (From Kistner.[7])

demonstrated in the higher magnification in Fig. 5, showing a few normal decidual cells at the right and necrotic cells in the midportion above the blood vessels and edematous cells at the upper left. Fig. 6 illustrates the same process in an area of vaginal endometriosis biopsied after 12 weeks of continuous therapy with a mixture of 17-alpha-ethinyl-17-hydroxy-5-10-estren-3-one with 1.5 per cent ethinyl estradiol-3-methyl ether. The same process of decidual necrosis and edema is evident. Figs. 7 and 8 show this process in greater detail.

Four progestins are presently available for use in the treatment of endometriosis. They are (1) 17-alpha-hydroxyprogesterone caproate,* (2) 17-alpha-ethinyl-17-hydroxy-5-10-estren-3-one (norethynodrel) with 1.5 per cent ethinyl estradiol-3-methyl ether,* (3) 6-alpha-methyl-17-alpha hydroxyprogesterone acetate (medroxyprogesterone),† and (4) 17-alpha-ethinyl-19-nortestosterone (norethindrone).‡ Each of these preparations will be considered in detail in regard to dosage, side effects, and specific advantages and disadvantages in individual patients.

1. 17-alpha-hydroxyprogesterone caproate (Fig. 9). The first patients treated in our series received a combination of diethylstilbestrol (5.0 mg.) or ethinyl estradiol (0.05 mg.) daily, plus 17-alpha-hydroxy-progesterone caproate (62.5 mg.) weekly for a pe-

*Delalutin, E. R. Squibb & Sons.

*Enovid, G. D. Searle & Company.
†Provera, The Upjohn Company.
‡Norlutin, Parke, Davis & Company.

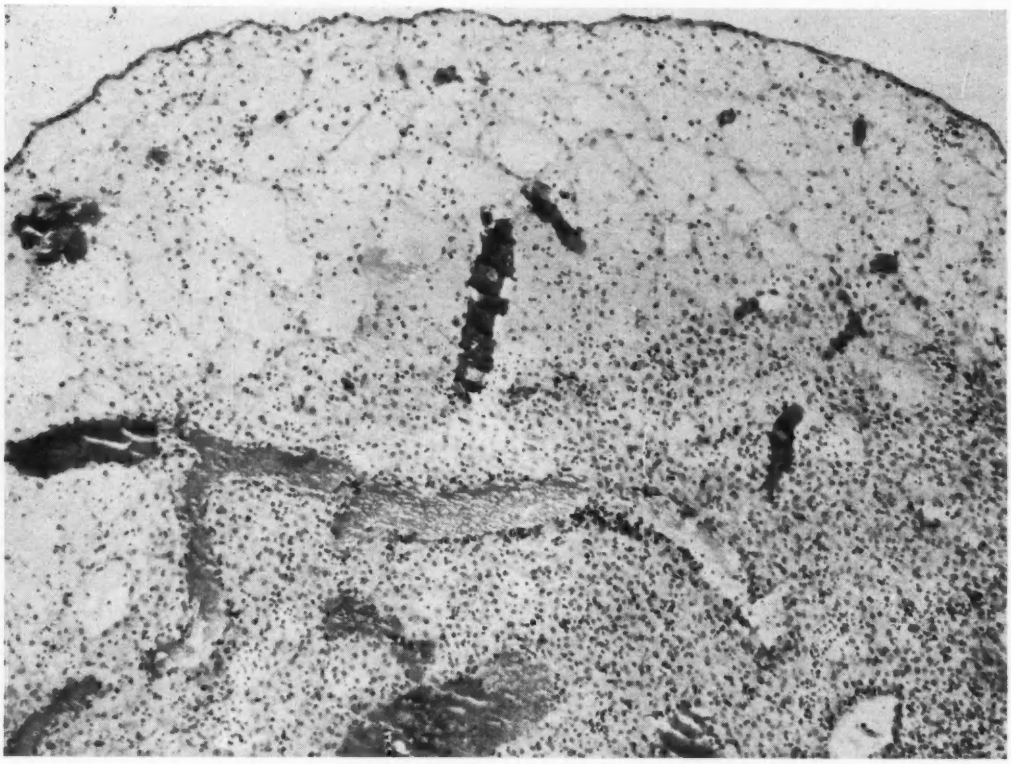


Fig. 4. FHW S-57-528. Endometrial biopsy after 15 weeks of increasing doses of norethynodrel with ethinyl estradiol. There is a variation in response in the separate levels of the endometrium. Note the marked edema and decidual necrosis under the surface epithelium. In the mid-zone there is moderate intercellular edema and minimal necrosis of decidual cells. The basalis is made up of compact, well-preserved decidual cells. (×50; reduced 1/6.) (From Kistner: Clin. Obst. & Gynec. 2:884, 1959.)

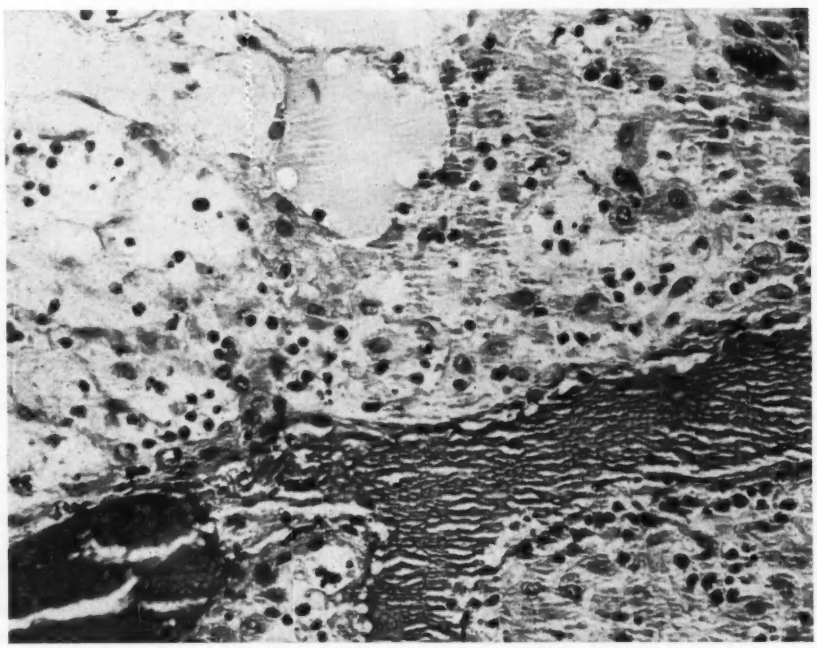


Fig. 5. FHW S-57-528. Higher power of endometrial biopsy in Fig. 4, to show in detail the marked intercellular edema. This is seen best at the upper left part of the photograph. Necrotic decidual cells may be seen above the dilated blood vessel. (×150; reduced 1/3.)

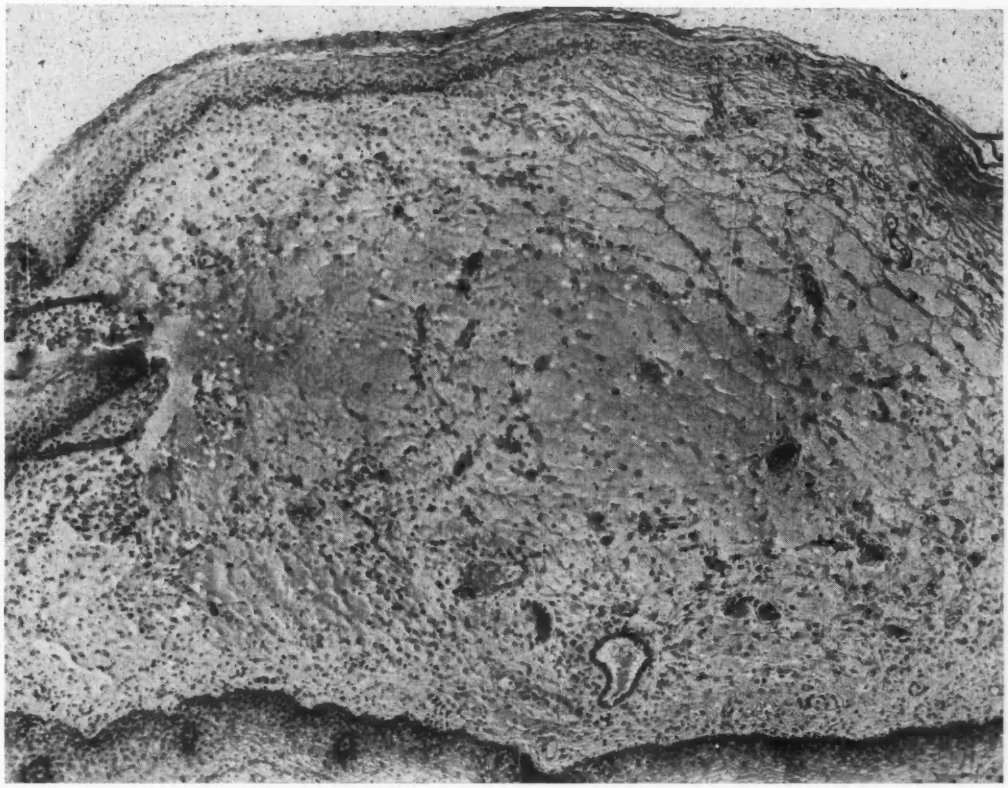


Fig. 6. FHW S-58-3435. Biopsy of an area of vaginal endometriosis after 12 weeks of continuous norethynodrel with ethinyl estradiol therapy. There is evidence of a marked generalized edema throughout the endometriosis. Under the vaginal epithelium the decidua is well maintained but most of it is undergoing necrosis. One inactive gland is seen near the bottom of the section. (×50; reduced 1/7.) (From Kistner: Fertil. & Steril. 10:549, 1959.)

riod of 2 weeks. This is gradually increased every 2 weeks so that at the end of 12 weeks the patient is receiving 500 mg. of 17-alpha-hydroxyprogesterone caproate. The estrogen is increased at weekly intervals so that at the end of 12 weeks a daily dose of 60.0 mg. of diethylstibestrol or 0.6 mg. ethinyl estradiol is being administered. A later variation of this schedule is to give estradiol valerate* intramuscularly in a dose of 1 c.c. (10 mg.) weekly for 2 weeks with an increase of 0.5 c.c. every 2 weeks.

Several of the patients treated with 17-alpha-hydroxyprogesterone caproate and estradiol valerate developed rather severe uterine cramps, and "break-through" bleeding necessitating cessation of therapy. The apparent difficulty is in the determination of the correct proportion of estrogen to progestin, since when excess estrogen is given the production of decidua is excessive and its vascularity markedly increased. Improved results have been obtained with a combination of 17-alpha-hydroxyprogesterone caproate (250 mg. per cubic centimeter) and estradiol valerate (5 mg. per cubic centimeter). This mixture* has been used extensively by Thomas and co-workers.[12] His results have been comparable to those of other investigators utilizing oral progestins, namely, an 85 per cent over-all improvement rate.

The use of the mixture offers the definite advantage of a constancy of absorption as

*Delestrogen, E. R. Squibb & Sons.

*Deluteval, E. R. Squibb & Sons.

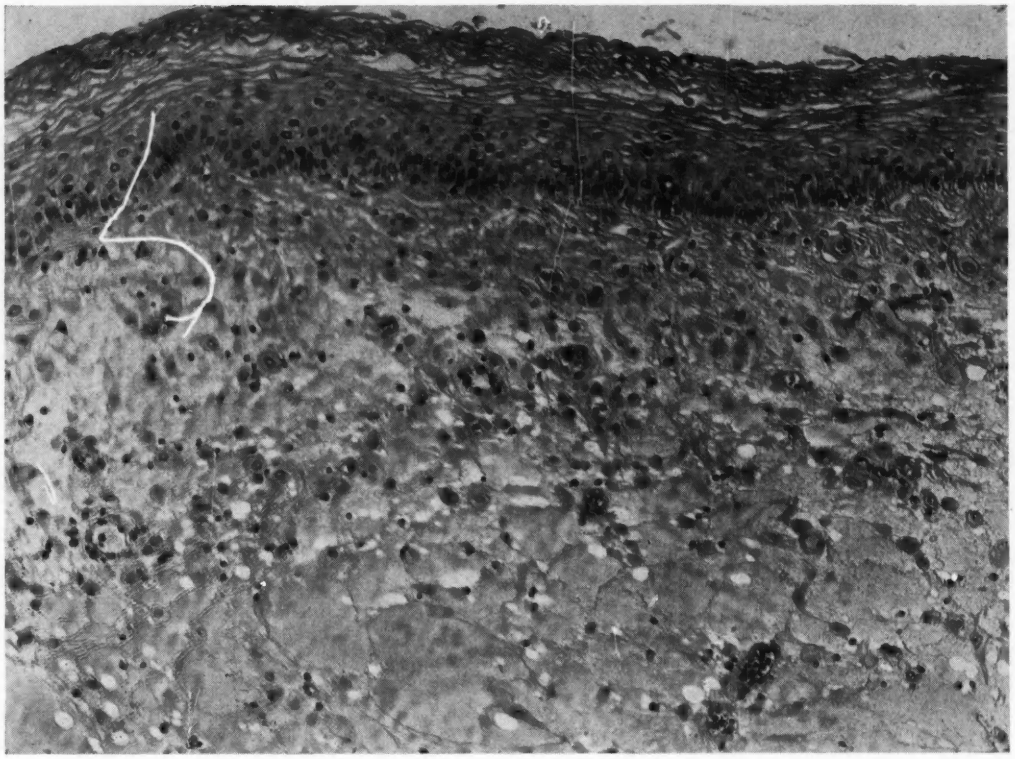


Fig. 7. FHW S-58-3435. Higher power of an area seen in Fig. 6. The well-differentiated decidual cells are seen to lie immediately under the surface epithelium, and the intercellular edema and decidual necrosis are evident near the bottom. (×100.) (From Kistner: Fertil. & Steril. 10:549, 1959.)

a result of parenteral administration. Injections may be spaced at intervals of 2 weeks and the dose held constant until "break-through" bleeding occurs. The tendency toward nausea in the early part of the pseudopregnancy is diminished and the difficulties of oral administration are obviated. This progestin is a caproate ester of hydroxyprogesterone and is not a so-called "19-nor-compound." Its androgenic potential is, therefore, less than that of some other available progestins. It is not contraindicated during early pregnancy.

2. 17-alpha-ethinyl-17-hydroxy-5-10-estren -3-one (norethynodrel) with 1.5 per cent ethinyl estradiol-3-methyl ether (Fig. 10).* The majority of the patients in our series have been treated with this preparation. They now number well over 100 and the improvement rate has remained at approximately 80 to 85 per cent. The dose schedule is as follows: 10 mg. daily for 2 weeks with an increase of 10 mg. every 2 weeks up to a maintenance dose of 30 or 40 mg. daily. The major side effects have been nausea, breast soreness, vaginal discharge, and fluid retention. Nausea may be diminished by beginning with a 5 mg. rather than a 10 mg. tablet or by giving milk, an antacid, a tranquilizer, or an antiemetic drug with the medication. The nausea seems related to the estrogen content of the mixture (it is rare with norethindrone). Fluid retention may be diminished by a low-sodium diet and the intermittent use of chlorothiazide. A few patients have complained of insomnia, restlessness, and irritability whereas others have noted excessive lethargy and a "tired" feeling. Severe and persistent headaches have necessitated the cessation of treatment in 2 patients. "Break-through" bleeding has been infre-

*Enovid.

quent and has responded to increased doses. In some patients, however, it has been necessary to increase the total daily dose to 60 or 70 mg. daily to accomplish this. The obvious difficulty with such a schedule is the cost.

Pseudopregnancy should be continued for a minimum of 6 months and if endometriosis is extensive, therapy should be extended to 9 to 12 months. Remissions have occurred but, to date, have been noted in patients treated for less than 6 months. Four separate groups of patients have been treated: (1) those without previous surgery for endometriosis (most of these had a definitive diagnosis by culdoscopy), (2) those with a previous conservative laparotomy who developed recurrent disease, (3) those treated "prophylactically" after a conservative laparotomy, and (4) those with vaginal endometriosis. The relationship of subsequent fertility to pseudopregnancy cannot be adequately correlated at this time. When patients did become pregnant after the therapy they did so within 3 to 6 months. This is an improvement upon the interval of 2.7 years noted in a series of 138 patients treated at the Free Hospital for Women by operation alone.[1]

Some question has been raised about the ability of patients who have undergone prolonged pseudopregnancy subsequently to ovulate. All patients who have been followed after treatment by either basal body temperatures or endometrial biopsies have given evidence of spontaneous ovulation within 6 to 8 weeks. Similar evidence is available from a much larger series of Rock, Garcia, and Pincus[10] where ovulation was inhibited for over 30 cycles in the Puerto

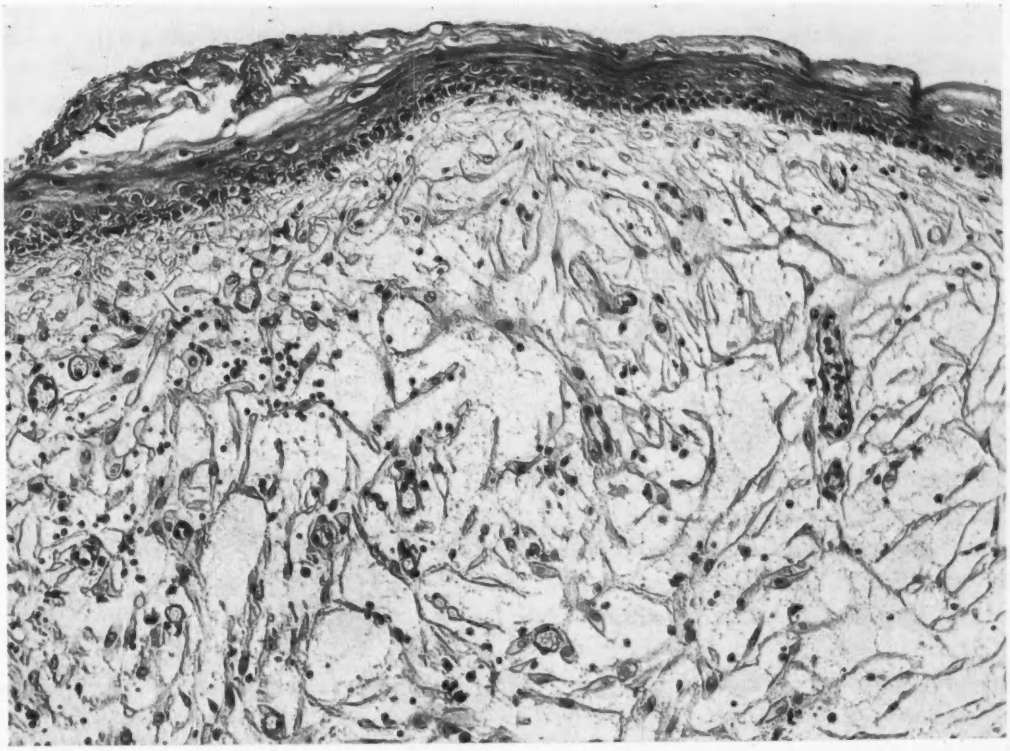
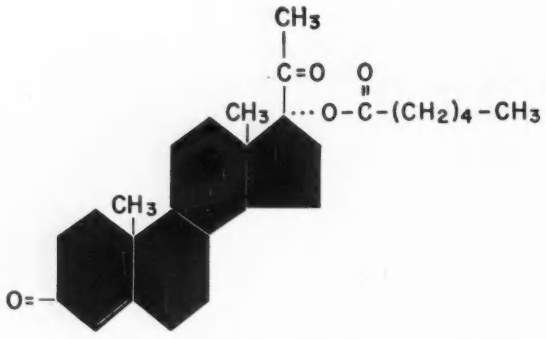


Fig. 8. FHW S-58-3435. Higher power view of vaginal biopsy seen in Fig. 6. There is an unusual pattern of decidual change with most decidual cells remaining as "naked nuclei" or as cytoplasmic strands in an edematous stroma. A few lymphocytes and macrophages are present and suggest an "absorptive" process of the necrotic endometriosis. (×100; reduced 1/6.) (From Kistner: Fertil. & Steril. 10:549, 1959.)



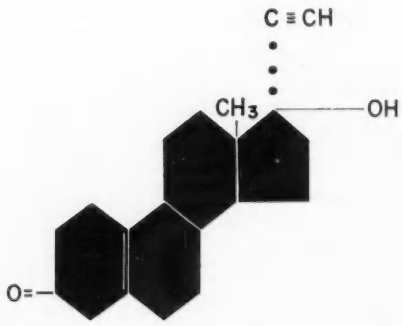
[17 alpha-hydroxyprogesterone caproate]

Fig. 9. Structural formula of 17-alpha-hydroxyprogesterone caproate. The esterification of the relatively inactive hydroxyprogesterone at the 17-alpha position results in a compound which has an increased potency of thirty times with a five-fold increase in duration.

Rico contraception study. Ovarian biopsies obtained subsequently to cessation of long-term therapy have shown no morphologic evidence of disturbance in the number or development of Graafian follicles.* The estrogen present in the mixture may stimulate the growth of leiomyomas and if this occurs another preparation should be substituted.

Hirsutism, acne, and lowering of the voice have not been noted during prolonged pseudopregnancy. This may be due to the fact that the drug is a derivative of a basic C-18 (estrane) nucleus with the double bond present in the 5-10 position in the "A" ring (Fig. 10). Norethynodrel has been shown to be much less androgenic in animal experiments than some of the other progestins where the double bond is in the usual 4-5 position as in testosterone. Its use during early pregnancy is not contraindicated.

3. *6-alpha-methyl-17-alpha-hydroxyprogesterone acetate (medroxyprogesterone) (Fig. 11).* This preparation is one of the newer progestins and is available in tablets of 2.5 and 10.0 mg. and for intramuscular use in a concentration of 25 and 50 mg. per cubic centimeter. The oral preparation is an extremely potent progestin and has been shown to be effective in maintaining pregnancy in ovariectomized rats. Furthermore, it is an effective inhibitor of ovulation and is very mildly estrogenic in animal experiments. If given in high enough doses it produces some stimulation of the secondary sex characters of the castrate male test animal. Like progesterone it causes a very slight degree of sodium retention in the adrenalectomized rat. Intramuscular medroxyprogesterone is also a potent progestin: one 50 mg. injection will produce secretory change in the endometrium within 6 or 7 days. Furthermore it is long acting: one 50 mg. injection will give a temperature rise which lasts 4 to 6 weeks. Progestational effects in the postmenopausal female have been noted in the endometrium 6 weeks after one injection of 100 mg. Although medroxyprogesterone is a potent gonadotrophic inhibitor and will delay ovulation and menstruation, it is necessary to add small amounts of estrogenic substances if a prolonged pseudopregnancy is desired. Our method has been to give 100 mg. intramuscularly every 2 weeks in conjunction with ethinyl estradiol, 0.05 mg. daily.



[17-α-ethynyl-17 hydroxy-5 (10) estren-3-one]

Fig. 10. Structural formula of norethynodrel. Note the double bond in the 5-10 position in the "A" ring. Enovid contains 1.5 per cent ethinyl estradiol-3-methyl ether in addition to this progestin. This preparation is a potent oral progestin with minimal androgenic properties.

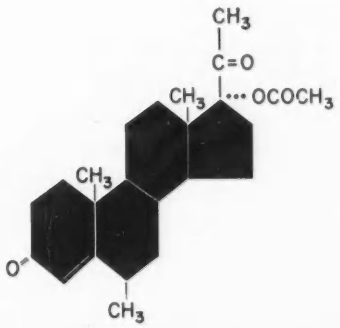
*McKay, D. G.: Personal communication.

The oral estrogen may be gradually increased every 2 or 3 weeks or one may await the development of spotting or bleeding before increasing the dose.

Greenblatt and Barfield[4] have noted satisfactory results in the treatment of extensive endometriosis with the oral preparation and an added estrogen. Signs of androgenicity did not occur after prolonged treatment nor was "break-through" bleeding particularly troublesome. Their over-all improvement rate has been reported as 75 per cent. We have used medroxyprogesterone in 8 cases of extensive endometriosis. The results were excellent in each instance.

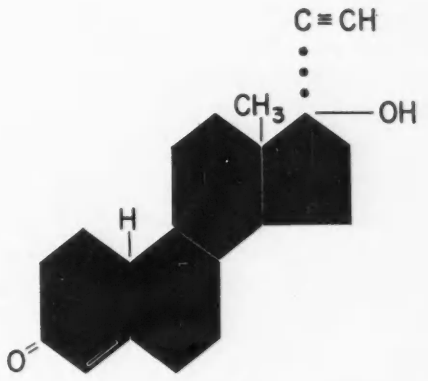
4. 17-alpha-ethinyl-19-nortestosterone (norethindrone) (Fig. 12). This preparation is a true "19-nor testosterone" and resembles the oral progestin, ethinyl testosterone (anhydrohydroxyprogesterone), which differs from norethindrone in that the methyl group on carbon 19 is still present. Norethindrone is a potent oral progestin with essentially the same properties as norethynodrel except that, in animal studies, it has an increased androgenic potential. Greenblatt and co-workers have used norethindrone in over 40 patients with endometriosis and noted an improvement rate of approximately 75 per cent.[11,12] The duration of therapy varied from 7 to 9 months with doses ranging from 20 to 50 mg. daily. Barfield* described hirsutism associated with the prolonged use of norethindrone to be "mild, but not infrequent" and deepening of the voice as a rare side effect. Edema and weight gain were noted in about the same degree as with norethynodrel with ethinyl estradiol, but breast soreness and nausea were not described. The latter symptoms are undoubtedly associated with the estrogen content of norethynodrel with ethinyl estradiol. Thus if nausea is troublesome during the early phases of norethynodrel with ethinyl estradiol pseudopregnancy, norethindrone may be substituted. Conversely, if hirsutism seems to be progressive while norethindrone is being administered, it may be replaced with norethynodrel with ethinyl estradiol.

Lebherz† has treated 26 patients at the U. S. Naval Hospital at Bethesda during



[6-methyl-17-alpha-hydroxy-progesterone acetate]

Fig. 11. Structural formula of 6-alpha-methyl-17-alpha-hydroxyprogesterone acetate. Medroxyprogesterone differs from a hydroxyprogesterone preparation, in the addition of a methyl group at position 6 in the "B" ring. Animal tests have shown that medroxyprogesterone given orally is 60 to 75 times as potent as oral 17-alpha-hydroxyprogesterone acetate and 2 to 3 times as potent as parenteral progesterone. Medroxyprogesterone has few or no estrogenic or androgenic properties in the human female.



(17-alpha-ethinyl-19 nortestosterone)

Fig. 12. Structural formula of 17-alpha-ethinyl-19-nortestosterone (norethindrone). Note the absence of the methyl group from carbon 19, thus making it a "19-nor" testosterone. The ethinyl radical is in the alpha position on the 17 carbon as it is in norethynodrel.

*Barfield, W. E.: Personal communication.
†Lebherz, T. B.: Personal communication.

the last 2 years with norethindrone. His dosage schedule was similar to that noted above. Lebherz noted, however, a rather high incidence of side effects due to the androgenicity of the preparation. Hirsutism was noted in 2 patients and acne in 3. Increased libido was described by 10 patients and "break-through" bleeding occurred in 20 of the 26 patients. The latter finding is due, in the opinion of the author, to the absence of sufficient estrogen in the compound to maintain the endometrium.

An acetic acid ester of 17 alpha-ethinyl-19-nortestosterone (norethindrone acetate) has recently been introduced and its effectiveness in patients with endometriosis evaluated by Bushnell[3] and Kupperman.[8] Laboratory studies by Junkmann[5] have demonstrated that this compound is identical in physiologic activity with the parent alcohol, differing only in being several times more potent milligram for milligram. Clinical experiments in the human have indicated an increased potency of the acetate over norethindrone in the order of 2:1. Bushnell reported marked subjective and objective improvement in 10 patients. Three of these were completely free of palpable tumors and in the remaining 7 there was a marked reduction of pelvic swelling and pain. A dose of 10 mg. daily was continued uninterrupted for several months in these patients. Kupperman has reported excellent results using 15 mg. daily of the acetate (or 30 mg. norethindrone) for 6 to 9 months with freedom from symptoms for extended periods following discontinuation of the medication. The incidence of side effects in these latter studies is not known. We have had no personal experience with norethindrone in the treatment of endometriosis. Wilkins has suggested[13] that norethindrone should not be administered during early pregnancy because of its androgenic potential.

Summary and conclusions

The use of the various new progestins in the treatment of endometriosis seems to be of definite therapeutic value. Reports of at least six separate investigators have indicated an improvement rate of between 75 and 85 per cent. Although remissions in certain patients have lasted as long as 30 months, definite conclusions cannot be drawn regarding the degree of permanent relief afforded.

The rationale of this regimen differs from those previously described in that a decidual response in areas of endometriosis (together with amenorrhea) is suggested as being responsible for both the subjective and objective improvement. Each of the four progestins discussed has been shown to induce an adequate decidual response both in the endometrium and in areas of endometriosis.

In order to secure a pseudopregnancy it is necessary to administer both estrogens and progestins in increasing dosage. The amount of estrogen must be kept at a rather low level but is necessary to prevent "break-through" uterine bleeding. An excess of estrogen results in disturbing nausea at the onset of treatment, breast tenderness, and excessive vaginal discharge. Long-acting, parenterally administered progestins have the advantage of constancy of dose and absorption. The caproate and acetate esters of 17-alpha-hydroxyprogesterone are effective but must be given with adequate estrogen. Norethynodrel with ethinyl estradiol has given excellent results in over 200 patients with proved endometriosis. The only disadvantage seems to be the occasional side effect of the estrogen. This may be combated by initiating therapy with smaller doses. Norethindrone has the disadvantage of occasionally causing hirsutism and facial acne.

References

1. Bacon, W. B.: Results in 138 Cases of Endometriosis Treated by Conservative Surgery, Am. J. Obst. & Gynec. **57**:953-958, 1949.
2. Beecham, C. T.: Letter to the editor, J.A.M.A. **163**:678, 1957.
3. Bushnell, L. F.: In Gajewski, J. E.: Medical Summary, Norlutin Acetate, Parke, Davis & Company.

4. Greenblatt, R. B., and Barfield, W. E.: Brook Lodge Invitational Symposium on Progesterone, Kalamazoo, Mich., Nov. 21, 1959.
5. Junkmann, C.: Unpublished reports cited by H. Werner-Boschann, Ann. New York Acad. Sc. **71**:727-752, 1958.
6. Karnaky, J. K.: Endometriosis, in Conn, H. T.: Current Therapy, Philadelphia, 1957, W. B. Saunders Company, pp. 676-677.
7. Kistner, R. W.: The Use of Newer Progestins in the Treatment of Endometriosis, Am. J. Obst. & Gynec. **75**:264-278, 1958.
8. Kupperman, H. S.: In Gajewski, J. E.: Medical Summary, Norulin Acetate, Parke, Davis & Company.
9. Meigs, J. V.: The Medical Treatment of Endometriosis and the Significance of Endometriosis, Surg. Gynec. & Obst. **89**:317-321, 1949.
10. Rock, J., Garcia, C. R., and Pincus, G.: Conference on Enovid, Searle Research Laboratories, November, 1958.
11. Scott, R. B., and Wharton, L. R., Jr.: The Effect of Testosterone on Experimental Endometriosis in Rhesus Monkeys, Am. J. Obst. & Gynec. **78**:1020-1027, 1959.
12. Thomas, H. H.: The Conservative Treatment of Endometriosis With Delalutin and Delestrogen, Long Acting Ovarian Steroid Hormones, read before the District VII meeting of the American College of Obstetricians and Gynecologists, Jackson, Miss., Sept. 13, 1958.
13. Wilkins, L.: Masculinization of the Female Fetus Due to Use of Orally Given Progestins, J.A.M.A. **172**:1028-1031, 1960.

The mainspring of scientific progress is not uniformity, but independence of thought translated into experimental action, and individuality is one of the most precious, stimulating, and necessary qualities of an efficient investigator. It would seem that Nature does not yield her secrets to groups, but to individuals who have the nous *first to formulate the right question, and then to ask it in the correct experimental manner. Nature is very particular about the last; she only answers when compelled to do so.*

From "The Spirit of Research—A Plea for Independence" by Mervyn Gordon, Lancet **1**:807, June 30, 1945. Reprinted From St. Bartholomew's Hospital Journal, for June, 1920.

Book reviews

Clark's Applied Pharmacology, A. Wilson and H. O. Schild. Boston. 1959, Little, Brown & Company. 750 pages. $10.00

The modern American textbook of pharmacology may frighten a prospective reader because of its size and its cost, but America has no small and inexpensive book of merit. In this country all textbooks of pharmacology attempt encylcopedic coverage of this vast and fast-moving field. The British, however, have managed to cope with the problem with considerable economy, both verbal and physical, so that one approaches a new edition of such a classic as *Clark's Applied Pharmacology,* which is about one-third the size and half the cost of the American prototype, with the hope that it will also be useful on this side of the Atlantic.

The current edition of Clark is the ninth. It is 60 pages longer than the eighth and each of the 750 pages is slightly larger. That Andrew Wilson and H. O. Schild should have been able to deal with the advances of the past seven years with such a modest bulge is, in itself, a major accomplishment.

As in previous editions, the writing is clear and concise; it has to be if the subject is to be contained in a portable book. But there is another way to save space which I would recommend. I suggest that the assumption be made that the reader of a text on pharmacology either has an adequate background in physiology or will refer to a good book on the subject if he needs it. Apparently neither American nor British textbook writers will take the chance. Each deals with the physiologic basis of the pharmacologic issues in its own way; for the most part inadequately. In Clark most, but not all, physiologic discussions are compressed almost, but not quite, to extinction; the revisers were not able to go all the way. Thus, in the chapters on the pharmacology of the kidneys and the pharmacology of respiration, it is the pharmacology which suffers from compression. Another way of reducing the size of textbooks of pharmacology is to omit the invariably inadequate discussions of therapeutics. This cannot be done here since Clark's is an applied pharmacology, but therapy is satisfactorily reduced to a minimum.

However well written and lucidly presented the material in this book may be, it sometimes suffers from the limitations of space; thus, especially in view of their cur-

rent importance, the discussion of the adrenocortical steroids seemed unduly brief. But opinions on the proper allocation of spact to particular subjects are often based on highly personal prejudices, reviewers' as well as authors'. It must be stated, therefore, that the book covers the field of pharmacology remarkably well for its format. The chapters on anesthetics and the pharmacology of the female reproductive system are outstanding. There are also new chapters on the chemotherapy of tuberculosis and on psychopharmacology which are likewise excellent.

I would be tempted to recommend this book to our students were it not that they find the proper American names for drugs confusing enough without compounding this difficulty with British versions not in use here. Although this issue has nothing to do with the merit of the book, it brings up a problem which pharmacologists have to face and should take an active part in resolving. Surely it is nothing short of ridiculous that a drug should have a different name here and in England, but there are many such; both old drugs and new ones. Although these differences do not seem oppressive as one views the book as a whole, they are an irritation even though the American equivalents are often furnished. It is therefore only to those on the other side of the Atlantic that I can give my unreserved recommendation to this excellent small book on a big subject. A pity!

Walter Modell

The Measurement of Subjective Responses; Quantitative Effects of Drugs, Henry K. Beecher. New York, 1959, Oxford University Press. 494 pages. $12.75.

Professor Beecher, in the preface, clearly states the fundamental proposition to which the present monograph bears principal reference: it is—as he puts it—the proposition that "subjective responses, symptoms, can be expressed in quantitative terms." Plausibility and validity of this statement can be examined in different ways; Professor Beecher successfully chooses the pragmatic attitude, and records lucidly and systematically the impressive results that can be obtained when this proposition is made the basis for appropriately designed and conducted measurement of drug action in (chiefly diseased) man.

As prototype for the quantitative study of subjective responses, the measurement of pain is selected. This broad topic occupies approximately one-half of the entire book; it also contains chapters on placebo and placebo reactors, drug interactions, and on the relevant statistical methods (the latter prepared by Professor F. Mosteller). The well-conceived organization of the presented material, the uniformly concise style, and the fair, yet uncompromising, presentation of conflicting views let the author's own opinions and conclusions clearly emerge, and place them in their proper context and perspective. Evidently, Professor Beecher's approach to the measurement of pain and analgesic drug action rests on two basic assumptions: (1) pain cannot be defined except introspectively; (2) there is a fundamental distinction between the psychic reaction component to tissue damage, and pain perception.

Considerable evidence is adduced to demonstrate the pragmatic value of these assumptions in the measurement of analgesic drug action. In this context, Professor Beecher introduces the idea of the "significance" of tissue damage, and of its relation to the susceptibility of the pain-reaction component to analgesic drug action. It did not become clear to me in what way the significance of tissue damage is determined, and on what it depends. I wonder whether we are not led into a circular and purely verbal definition, and whether the primary fact is not susceptibility to drug action; this given, the original reaction pattern would then be attributed to "significant" tissue damage.

To the pragmatic value of decomposing pain into a psychological and physiologic category can be added neurophysiologic plausibility derived from recent work on attention, habituation, and other forms of "editing" in sensory pathways. Such supporting arguments are not fully exploited in Professor Beecher's account.

The eminent success of the two principal premises stated before (and of the postulates derived from them), used in conjunction with appropriate controls and statistical design, is well illustrated by the results of analgesic potency measurements of Professor Beecher and his group, and of other workers in the field. The precision of these results makes a strong case for the utility of this approach, conceptual as well as in terms of the procedures used. At the same time, questions may come to one's mind regarding the epistemologic validity of the "measurement of subjective responses," and how exactly such an approach can be integrated into more conventional views on perception on the one, and on measurement on the other, hand. Professor Beecher does not get involved in the discussion of such aspects. Yet I believe that clarification of these issues can greatly strengthen his case. At first sight, it may seem strange that numerical values can be ascribed to private sense data. However, the actual act of measurement is one of ranking into more or less of some sense datum, and numerical values are derived from performance of the ranking procedure in populations rather than from measurements in individuals. It would, thus, seem to me that the quantitation is ultimately derived from a topologic, rather than a metric measure. Accordingly, the rules of measurement conform to the structure of sense data (J. R. Smythies) as opposed to the metrics of physical objects, and it appears to me that it is this very aspect of Professor Beecher's approach in which resides its superiority as compared with the "physicalistically" oriented trends in the quantitation of pain.

In part II, the author applies the principles of measurement of pain, and its relief, to other subjective responses elicited by drugs. In a chapter on "mental clouding and other subjective effects of morphine," the usefulness of nonparametric statistics for the evaluation of mood and sensation data is clearly demonstrated. Similarly, sedative and hypnotic states, effects of anesthetic substances, euphoria and dysphoria, pruritus, expressions of anxiety, and cough are analyzed. In these chapters, Professor Beecher draws extensively on the material published earlier in various journals by himself and members of his group. Particularly in reading the chapter on psychmimetic drugs, one may be impressed with the discrepancy between scarcity of presently available quantitative data in man, and the potential usefulness of Professor Beecher's approach for further explorations. I do, however, wonder whether further quantitative work on "psychmimetica" will not raise new aspects for which work on pain cannot serve as a complete prototype: in the measurement of pain, the reaction component of the subject is revealed to the observer through essentially predicative verbal reports, and verbal communication between subject and observer can obviously be made to operate so smoothly that Professor Beecher did not find it necessary to examine more closely this link in the measuring process. On the other hand, psychmimetic agents are likely to evoke in the subject experiential situations for which no adequate linguistic expression may be available, and which may be more prone to distortion by the attempt to fit them into the mold of verbal reports.

This monograph assembles, and organizes into a coherent system, a body of knowledge which, in my mind, convincingly proves that pharmacology, as a quantitative science, can successfully expand into the domain of introspective data, and, conversely, that the exploration of subjective responses to drugs constitutes an integral part of pharmacology; it, furthermore, corroborates with powerful arguments and examples the premise of clinical pharmacol-

ogy, namely, that "the sick man serves as the only final experimental subject."

Gerhard Werner

Psychopharmacology—Problems in Evaluation, J. O. Cole and R. W. Gerard, editors. Publication 583, National Academy of Sciences, Washington, D.C., 1959.

In September, 1956, the National Institute of Mental Health, The National Academy of Sciences–National Research Council, and the American Psychiatric Association jointly sponsored a conference on the evaluation of pharmacotherapy in mental illness. The present volume, published in 1959, records the formal papers and discussions of this conference.

In part I, eight review papers summarize competently the pharmacologic, behavioral, and clinical observations with the new agents for drug treatment of mental diseases. In the preparation for the symposium, these reviews constituted working papers; they were presented in January, 1956, to a planning group which decided that five committees should be formed to deal with the different aspects of evaluation in psychopharmacology: one was to explore methods for preliminary screening of drugs with actions on the central nervous system; three committees were to discuss considerations pertinent to the clinical evaluation of drugs in psychiatry; a fifth committee was put in charge of considering plans for implementation of policies which would emerge from the individual sections of the program. Papers and discussions on these topics constitute by far the larger part of the published symposium (parts II to VI).

It will be apparent that the content of this volume can be divided into two broad categories: part I is essentially a systematic coverage of existing data up to the time the conference was held. The papers of this section fulfilled their function by setting the stage for the conference, but it is in the nature of most papers in this category to become rapidly outdated. More important for the reader of the printed symposium are the subsequent sections since they present a thorough examination of methods, relevance, and validity in the diverse areas of psychopharmacologic investigations. From formal papers and well-directed (and edited) discussions emerge general principles of research design in psychopharmacology which cannot fail to influence profoundly the standards of psychopharmacologic inquiry.

Gerhard Werner

Clinical Disorders of Hydration and Acid-Base Equilibrium, second edition, L. G. Welt. Boston, 1959, Little, Brown & Company. 336 pages, 766 references to the literature. $7.00.

Rumor has it that in this day and age no patient is allowed to die in our advanced institutions unless in perfect electrolyte balance. Patients are not to apply to St. Peter at the Gate with electrolyte disturbed; homeostasis has become the password to the next world.

The complicated subject of fluid, anions, and cations is dealt with very competently by Dr. Welt in this scholarly work. The physiologic background is done well and many clinicians will find this as well as the clinical section instructive and of immediate practical value. However, all is not sweetness. Reading the chapter on renal physiology requires great concentration and much thought. The author delights in using many words when few will do; clauses are thrown together to "form" sentences. For example, on page 63: "The amazing discrimination and genius of the value judgments achieved by this organ are responsible, in great part, for the ability of the organism to survive the ordinary vicissitudes of life and the more compli-

cated problems imposed by the stress of disease." One knows what the author is trying to say, yet it is not clear at the first or second reading, and must be puzzled out. Frequently one is left wallowing in a proximal or distal tubule, not knowing in which direction the osmotic gradient is pointing. Here is another example (page 91): "Orloff et al. point out that if the same quantity of solutes were abstracted from a larger volume of fluid that gains access to the distal tubule, the osmolality of the fluid would impose a greater osmotic restraint on the diffusion of water and promote an increase in the excretion of free water."

In the chapter by Dr. Robert W. Winters on special problems presented by the pediatric patient, one feels that, in addition to the principles elucidated, more space should be devoted to the practical management of the dehydrated infant or child. On page 156, one reads that 60 to 80 ml. per kilogram of isotonic sodium solution (including the amount of the initial infusion) should be given to infants with isotonic dehydration, but there is no indication regarding the time interval involved. One also feels that Dr. Winters should give at least one formula which physicans can use as a starting point (cf. page 160: ". . . small frequent feedings should be given of an electrolyte-glucose solution designed to provide maintenance requirement and to continue replacement of potassium deficits").

Dr. Welt is at his best in presenting cases chosen to illustrate different aspects of electrolyte imbalance. Anyone who thinks he really knows electrolytes should read this section, and then compare his thoughts with the comments of the author: few will fail to learn.

Some of this book can be simplified, grammar improved, and the text made more readable without detriment to the content. In any event, it is useful to clinicians of all ages. Knowledge of the contents will enable you to let your patients live or die in perfect intracellular and extracellular electrolyte balance.

Edel Berman

Books received

Buchborn, E., and Bock, K. D., editors: Diuresis and Diuretics (An International Symposium), Berlin, 1959, Springer-Verlag, 382 pages.

Luck, J. M., editor: Annual Review of Biochemistry, Palo Alto, Annual Reviews, Inc. 698 pages. $7.00.

Moser, R. H.: Diseases of Medical Progress, Springfield, Ill., 1959, Charles C Thomas, Publisher. 131 pages.

Ross, S. T.: Synopsis of Treatment of Anorectal Diseases, St. Louis, 1959, The C. V. Mosby Company. 240 pages.

Ryan, R. E., Thornell, W. C., and Von Leden, H.: Synopsis of Ear, Nose, and Throat Diseases, St. Louis, 1959, The C. V. Mosby Company. 383 pages.

Wolstenholme, G. E. W., and O'Connor, C. M., editors: Biochemistry of Human Genetics (Ciba Foundation Symposium), Boston, 1959, Little, Brown & Company. 347 Pages. $9.50.

Wolstenholme, G. E. W., and O'Connor, M., editors: Cancer of the Cervix (Ciba Foundation Study Group No. 3), Boston, 1959, Little, Brown & Company. 114 pages. $2.50.

Wolstenholme, G. E. W., and O'Connor, M., editors: The Lifespan of Animals (Ciba Foundation Colloquia on Aging, Volume 5), Boston, 1959, Little, Brown & Company. 324 pages. $9.50.

Wolstenholme, G. E. W., and O'Connor, C. M., editors: Virus Virulence and Pathogenicity (Ciba Foundation Study Group No. 4), Boston, 1960, Little, Brown & Company. 114 pages. $2.50.

Announcement

It is with great pride that this JOURNAL notes the participation of its Editorial Board in the important functions of maintaining the standards of the Pharmacopeia of the United States. At the decennial meeting in Washington, March 28, 29, 30, 1960, Dr. Arthur C. DeGraff was elected President of the United States Pharmacopeial Convention 1960-1970. Dr. Windsor Cutting was elected to the Board of Trustees of the Convention. Dr. Dale G. Friend, Dr. Arthur Grollman, Dr. D. A. Karnofsky, and Dr. Walter Modell were elected to the General Committee of Revision. Drs. Cutting, DeGraff, Merritt, Modell, and Vandam also served on the General Revision Committee of the United States Pharmacopeia XVI which was adopted at the decennial meeting of the Convention.